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DIAGNOSIS AND TREATMENT OF ACUTE OTITIS EXTERNA
AN INTERDISCIPLINARY UPDATE

Proceedings of a Roundtable Discussion
February 7, 1998
The Boulders, Carefree, Arizona

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INTRODUCTION

Each year, otitis externa affects 4 out of 1,000 Americans, occurring in people of all ages and both sexes. While a number of factors may predispose people to it, this common health problem is often called "swimmer's ear." It occurs most frequently in young adults, particularly during the warmer months, when water sports are popular. Otitis externa is a broad term for a disease state that includes inflammation or infection of the external auditory canal and auricle. It can range from mild inflammation and discomfort to a life-threatening disease.

Treatment of otitis externa is dependent on a thorough understanding of anatomy and physiology of the external ear canal, a knowledge of the microbiology of potential pathogens, and familiarity with the clinical presentation so that an accurate and timely diagnosis can be reached. Control of infection is predicated on frequent cleansing of debris from the external ear canal so that topical therapy can be effective.

Since otitis externa is seen by various specialties, this Roundtable Discussion included representatives from otolaryngology, pediatrics, family practice, and emergency medicine. The goal of the meeting was to review otitis externa and to discuss topics such as the definition of the disease, the cause and predisposing factors, and treatment guidelines, as well as to review a new treatment option soon to be available.

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Robert M. Guthrie, MD: I'd like to welcome everyone here. This is the first time in 25 years there has been a significant effort to bring a new player into the external otitis market. So we're really on the cutting edge of something that's going to be a very interesting evolution. Dr Bailey will give a "pre-presentation" on the definition of otitis externa.

Byron J. Bailey, MD: In talking about external otitis, it quickly becomes apparent that there is a long definition and a short definition. The short definition is inflammation or infection of the external ear, particularly the external ear canal. The long definition is that otitis externa is a spectrum or a family of fairly common and ubiquitous diseases that include, most commonly, acute bacterial external otitis, sometimes called swimmer's ear, and occasionally, localized infections like furuncles. Less commonly, we run into eczematous otitis externa, fungal external otitis, and, rarely, skull base osteomyelitis. So, we have a condition that is characterized by its severity — mild, moderate, or severe — and by its acuity — acute, subacute, or chronic.

Dr Guthrie: Are there other systemic factors that would come into play here, besides the traditional exposure to water in swimmer's ear?

Dr Bailey: Clearly, this involves a lot more than swimmer's ear. There are many predisposing factors, including fairly common skin disorders. Seborrheic dermatitis, when it affects the skin of the ear canal, is a major predisposing factor to external otitis. And of course, the really difficult cases are related to systemic diseases in immunocompromised patients, diabetics, and people who have had radiation therapy in the region of the ear canal. These cases are fortunately rare, but very severe.

David L. Witsell, MD: I think it would be important to include those patients with a tympanic membrane perforation and chronic otitis media with drainage in the ear canal as an inciting factor for otitis externa.

Dr Bailey: True, especially with children.

Dr Guthrie: Are there other risk factors we can think of, beyond this (the skin conditions, the exposure to moisture, and then perforation of the ear)? Trauma, for example?

Dr Bailey: Certainly, trauma to the ear from either the patient or physician who cleans the ear too aggressively, causing injury to the skin of the ear canal.

Stanford T. Shulman, MD: I think it's important to bring up the term malignant otitis externa. In the field of infectious diseases, this is of great concern, in elderly diabetics, for example. In pediatrics, the rare patient with immunodeficiency, usually related to cancer or cancer therapy, can develop, rarely, malignant otitis externa, which of course is a very severe illness.

Jo-Ann S. Harris, MD: Another group I see in the rehabilitation hospital is children with hearing aids and devices that incite microtrauma. That can become very difficult to treat with the hearing devices in place at the same time.

Dr Guthrie: So, there are a lot of other issues beyond typical swimmer's ear that impact here, and that lead to presentation. If the disease were simple, treatment would be — and often has been — successful, but we have other complicating factors. How is external otitis diagnosed?

Dr Bailey: It's usually a clinical diagnosis, of course, based on ear pain (or otalgia), edema, redness, and discomfort on moving the ear. One can see that the ear canal is much smaller because of the swelling, and one often sees some purulent exudate.

Dr Guthrie: Other clinical signs, besides examination?

Dr Witsell: Occasionally, it can be associated with lymphadenopathy, particularly if it's robust otitis externa. For what appears to be a rather localized, small infection, patients can suffer quite remarkably with pain, to the point of needing narcotics.

Dr Bailey: And, of course, for malignant external otitis, the presence of granulation tissue is an indicator.

Dr Guthrie: Are there differential diagnostic issues? Is there something else that could present with the combination of pain and exudate, besides external otitis, that we have to watch out for?

Joseph E. Dohar, MD, MS: One of the major difficulties at times is delineating whether the infection is based primarily in the external auditory canal, or whether it is a continuation of a process that is based in the middle ear, with a secondary perforation. Sometimes there is edema in the canal, and squamous debris, etc, obscuring the view of the tympanic membrane.

Dr Guthrie: In primary care practice, it is a big challenge to differentiate an external infection from a compromised middle ear infection that has perforated and filled the canal. With either, there is pain and exudative material.

Dr Dohar: In children, the other issue is distinguishing very bad otitis externa from coalescent mastoiditis. Sometimes they look very similar. I agree with you that they cannot necessarily be distinguished on clinical grounds. Then one relies on imaging technology. A computed tomography scan is used to look for a coalescent mastoid process.

Dr Witsell: The follow-up is important in these patients, because if otitis externa is treated and begins to get better, one may be able to see the tympanic membrane and diagnose chronic otitis media or a perforation of the tympanic membrane. So, follow-up is a very important part of the diagnosis and treatment of otitis externa.

Fuad M. Baroody, MD: Often, patients are misdiagnosed with otitis externa and media, when they only have externa, because the eardrum will have debris on it, and will appear dull. A good sign of whether the middle ear is healthy or not is trying to make the eardrum move on pneumatic otoscopy, provided the patient is not in too much pain, and the eardrum is not obscured by swelling. Good mobility of the eardrum, to me, is a good index that the middle ear is probably okay. Obviously, follow-up will sort this out.

Dr Guthrie: Are there any other diagnostic indicators that separate pure otitis externa from a complicated middle ear infection?

Dr Witsell: The immediate history can be an important clue. For example, has the patient been swimming? Do they use cotton swabs in the ear?

Dr Baroody: Yes. Otitis media, too, probably starts with some pain, and then drainage. When it's otitis media–based, the patient with otitis externa might have a history of drainage first. And then, within a day or two, pain on the outside. That would suggest that there might have been a perforation with drainage. An abrasion of some sort can precipitate the external component, which leads to excruciating external pain. Remember that a draining middle ear will not cause as much pain — because there's no pus under pressure — as in otitis media without drainage. So, when the ear is draining pus, there is usually not too much pain, unless there is mastoiditis or another issue. Then, a day or two later, the external symptoms start.

Dr Guthrie: As opposed to the immediate onset of pain and drainage at the same time, precipitated together, which would point toward a pure otitis externa?

Dr Baroody: Potentially.

Mark S. Weis, MD: I think when drainage follows fever defervescence, that's a good sign of ruptured otitis media.

Dr Guthrie: Do we see fever with otitis externa? It seems to be a more localized infection.

Dr Weis: Only if there is rapidly expanding cellulitis around the canal.

Dr Shulman: Or so-called malignant otitis externa, which is often associated with systemic signs and symptoms.

Dr Dohar: I know that we have used malignant otitis externa, as a term, commonly in the past. Am I wrong in thinking that the newer terminology is "necrotizing otitis externa"?

Dr Bailey: That has come into more common use, because of confusion with the term malignant.

Dr Guthrie: And the parameters for making that diagnosis would be...

Peter S. Roland, MD: Necrotizing external otitis is really an osteomyelitis of the temporal bone. One can subdivide it into two different sorts. The true malignant otitis externa or necrotizing external otitis as described by Ryan Chandler[1] is osteomyelitis that starts in the external auditory canal as a typical external otitis and spreads to the temporal bone, probably through the fissures of Santorini. It is almost limited to elderly diabetics, almost always with *Pseudomonas*. The osteomyelitis that develops in the skull base of immunocompromised people, either with human immunodeficiency virus (HIV) or undergoing cancer chemotherapy, is more likely to start in the middle ear as otitis media, and spread to the temporal bone, and is much more likely to have organisms other than *Pseudomonas* as the causative organism. The true malignant otitis externa that starts in the canal is virtually always *Pseudomonas*.

Dr Guthrie: So, in the older adult diabetic, the presenting symptoms would be fever? Pain in the temporal area?

Dr Roland: It's a clinical diagnosis of external otitis that fails to respond to conventional therapy, with persistent pain, and an elevated erythrocyte sedimentation rate, usually 70 to 100 or 120. The actual diagnosis depends on imaging, specifically technetium 99 in bone scanning. But as a practical matter, any external otitis in an elderly diabetic that fails to resolve with conventional therapy over a period of a week or so, with intense pain, is early temporal bone osteomyelitis.

Dr Guthrie: Until proven otherwise.

Dr Roland: I think even if the bone scan is negative, it would be appropriate to treat it aggressively, as though it were early malignant external otitis.

Dr Guthrie: What if you haven't gotten to that point, and you've got an elderly diabetic presenting with external otitis, would you try routine treatment first, to see if they clear before imaging?

Dr Witsell: I would. It depends on the clinical presentation. Certainly, eye pain, associated with ear drainage and ear pain, is a bad prognostic feature. Those patients need to be treated very aggressively.

Dr Dohar: Something Dr Bailey said earlier is very useful. That is, the clinical sign on physical examination that most alerts you is granulation tissue in the canal. Even if the patient is first presenting with evidence of copious granulation tissue within the external auditory canal, the diagnosis of necrotizing otitis externa would be more likely, and therefore, more aggressive treatment would be justified.

Dr Bailey: If it were an elderly diabetic, I would treat them with systemic therapy.

Dr Dohar: Now that we have oral fluoroquinolones, our readiness to treat diabetics aggressively is increased, as compared to the old days, when it necessitated intravenous therapy.

Dr Guthrie: Let's talk about different patient types. What kind of treatment and diagnostic challenges are there with a 1- or 2-year-old child with severe ear pain?

Dr Harris: In a 1- or 2-year-old child, you're not going to have the diagnosis of severe ear pain. You're going to have a crying, fussy child. In the young infant, you really don't have a history. You only have signs. The mother's report is almost always fussiness. The diagnostic challenge in this age group is always going to be distinguishing otitis media with perforation and drainage from true external otitis. Most children, at 1 or 2, do not get routine swimmer's ear, because they do not have as much head immersion in the water as older children do. Also, one doesn't find it as early, because they don't complain verbally, but perhaps rub the ear. I think, as a pediatrician, it would be my job to make sure they don't have otitis media, and not assume that it is otitis externa. With these smaller ear canals, trying to see the eardrum becomes even more problematic. One sign that sometimes is misconstrued in children is itchiness. Otitis can present as itchiness in the older child, before they tell you it's pain. And they're scratching the ear, and then you've got a continuing problem. But in a 1-year or 2-year-old child, in my view, the diagnostic challenge is to rule out otitis media.

Dr Guthrie: How helpful would be the presence or absence of fever on history at making that diagnosis? If the parent says the child has not felt warm, but has been pulling or digging at the ear and fussing, does that help direct you toward externa rather than media?

Dr Harris: Those signs would be helpful.

Dr Guthrie: In those situations, how often do you face the dilemma of being forced to treat for both?

Dr Harris: Not often.

Dr Shulman: I think that's unusual. Otitis media has a very high frequency in the first couple of years of life, and then rapidly drops off. This is probably the inverse of the frequency of otitis externa. And statistically, a child at 1 or 2 years of age with ear pain is much more likely to have otitis media than to have otitis externa. So I don't think it is a very common problem to distinguish one from the other in a young child, necessitating therapy for both.

Dr Dohar: I think otitis media that results in spontaneous perforation and goes on to cause secondary otitis externa is quite rare. The more common scenario is that children who have a tympanostomy tube in place, or a chronic perforation, develop drainage, and perhaps an exuberant inflammatory response. In those children, the systemic signs are actually not very helpful, because they rarely have pain from the otitis media, and they rarely have fever. If they have fever, it's low-grade, even though the inflammatory base of the process is the middle ear. So that is more difficult to sort out. We have had a fair number of children come in with a clinical picture that looks like coalescent mastoiditis. And they've had a longstanding history of otitis, because they have had tubes put in. They come in with postauricular erythema and edema. Sometimes the lobule is, in fact, protruding forward, which we think of as a classic sign of otitis externa. And then, on imaging, the mastoid actually looks pretty good. So, it really is just a skin process secondary to the middle ear process. And one treats it with topicals and possibly oral antibiotics.

Dr Guthrie: So, in general, in the younger child, the clinical and historical presentation makes it not that hard a diagnostic dilemma.

Dr Harris: The epidemiology of the diseases indicates that in a 1- or 2-year-old child, it is probably otitis media, unless there is an extenuating circumstance like a tube. When you have a chronically or recurrently draining tube, you treat for both.

Dr Baroody: I think it's important to bring up the point of good physical examination. I think it's the basis for proper diagnosis in a child of otitis media or externa. It's critical to be able to look at the external auditory canal. Often, the child might not complain, but if you push on the auricle and external ear, they're going to be "fussy." It is important to visualize the eardrum. Often there is wax and debris. But a good look is your best index to what is going on.

Dr Bailey: I think with otitis media, there's usually some association with nasal disease: a runny nose, upper respiratory tract infection, nasal allergy. With otitis externa, you usually don't have that.

Dr Guthrie: Yes, there would be no reason to have that correlation. At ages 4 and 5 — where the incidence, in my experience, begins to taper off — a patient complains of ear pain. They are tender to manipulation of the external ear. And they have purulent-looking material in the canal, often obscuring the drum. In the absence of systemic signs and symptoms, do you have major reassurance that this is not a combination infection, but is limited to the external canal?

Dr Dohar: No, because if the patient has a perforation or a tube, they rarely will have systemic signs, in either case. And that's just a function of the fact that you're draining the middle ear, which is the source of the infection. In fact, if the patient has a tube, you're probably going to suspect that this is a draining otitis media.

Dr Guthrie: In a person that has not had a chronic perforation or a tube, is the presentation of local signs and the absence of systemic signs reassuring to the primary care physician?

Dr Shulman: Well, it's the other way around. The presence of systemic signs would make one nervous. I have seen fever in rare cases. I think it's related directly to how widespread the inflammatory response is.

Dr Baroody: Those are the children that one would potentially send for a computed tomography scan. The ear looks bad, they're in extreme pain, and they do have a fever. It's not very common, but we do see them.

Dr Guthrie: But let's take the typical presentation of a 6-year-old in the middle of the summer, who comes in with marked ear pain, tenderness on examination, and purulent material in the canal without fever. Are you comfortable with calling that typical external otitis?

Dr Baroody: Yes.

Dr Guthrie: You won't be able to get a good look at the tympanic membrane because of the pain, and that's traditionally what we have treated empirically, with topical therapy.

Dr Bailey: And that's the right thing to do.

Dr Shulman: That's correct. I would echo what was said earlier about the absence of systemic signs, such as fever, being reassuring in that particular situation. That solidifies the fact that there is a simple externa problem, and one doesn't need to be too concerned about other issues at that point.

Dr Weis: What if we see the same presentation in the winter, assuming the child is not on a swim team?

Dr Guthrie: I would look for other predisposing factors. Are they traumatizing the ear canal?

Dr Weis: That's when follow-up becomes extremely important. You check back in 2 or 3 days, after you treat it topically as a local infection. Is the ear canal less swollen then? Can you see the tympanic membrane better?

Dr Guthrie: If you had that atypical winter presentation, would you be comfortable starting topical therapy, and doing follow-up?

Dr Witsell: I think so. It's important to remember, although the incidence of otitis externa goes down during the winter, children still have water exposure from baths and showers, and they may manipulate their ears. So it's not an unreasonable diagnosis.

Dr Shulman: I think the primary care physician faced with that kind of a patient can proceed conservatively, as we've just discussed, but should have, in the back of his or her mind, the consideration that if this doesn't resolve as expected, it conceivably could be a more serious disease process. In children, one of the classic illnesses is what used to be called histiocytosis X, which is now called Langerhans cell histiocytosis. This is a group of rare diseases that encompasses histiocytosis X, and Letterer-Siwe disease, and Hand-Schüller-Christian disease. These are histiocytic malignancies that classically present in childhood with external otitis. These are very rare. But in the child who is not responding to treatment, they have to be considered.

Dr Guthrie: I usually don't make my traditional swimmer's ear patient in the middle of summer come back for re-check if they get better. If you had a presentation in the middle of winter, would you see them in 2 to 4 days, so that you wouldn't miss something unusual?

Dr Witsell: These unusual disease processes probably occur sporadically throughout the year. So if a patient responds to topical therapy, be it winter or summer, I think the proof is in the clinical response. If a patient does not respond well in the summer, then they also deserve a follow-up visit, and reconsideration of the problem.

Dr Shulman: I agree, although, since classic swimmer's ear occurs much more commonly in the summer, a cohort of patients presenting in December is going to be relatively enriched for the rarer events. Nonetheless, the clinical response is really the key issue, and dictates further action.

Dr Bailey: It's important to point out that although we've had a lot of discussion about not being able to see the eardrum, in most cases you can, in external otitis. Generally, in an otolaryngologist's office, there is a microscope, and an opportunity to see the drum pretty well, and to clean the ear canal, so maybe there's a difference among specialties in how difficult it is to separate otitis externa from otitis media.

Dr Guthrie: How much trouble do you have, Dr Weis, in sorting these out?

Dr Weis: Very little. I would say 95% of the time, physical examination will yield a diagnosis. I'll tell you one issue I have with external otitis, and it is kind of a sad commentary on our society. I see a lot of adults milking otitis externa for narcotic analgesia. It is hard to tell who is really in pain. It's an issue for primary care, and I am sure in otolaryngology as well. Certainly in the emergency room, I have encountered this.

Dr Witsell: It's important to note that adults who have risk factors for head and neck cancer can present with ear pain, particularly if they have a throat cancer, and they may be requesting narcotic analgesia. It is important in those patients to get a history as to their risk factors for cancer.

Dr Guthrie: Are the presentation issues the same in adolescence as in childhood?

Dr Dohar: Pretty much.

Dr Harris: Yes.

Dr Guthrie: So it's the same pattern. Now we get into adulthood. I assume that the same water exposure risk factors are there. Do you find that there is a difference?

Dr Witsell: Adults sometimes traumatize the ears by using pens, pencils, or cotton swabs to clean out wax.

Dr Harris: I think we should clearly distinguish normal hosts from abnormal hosts. Children with mucocutaneous candidiasis have trouble with *Candida* infection. Also, children who are hyperactive can do a lot of damage that we may not know about. Even in the teenage years, we have to distinguish normal hosts from anyone with underlying conditions or diseases. Eczema is an important one; we don't see much psoriasis, but we do see eczema. When we talk about diagnostic implications and therapeutic indications, we always have to come back to the epidemiology of the disease, and the condition of the host.

Dr Witsell: One thing we forgot to mention, especially in the pediatric population, is foreign bodies in the ear canal.

Dr Guthrie: That's an interesting question for a primary care doctor. Would removing the foreign body put the child at risk for otitis? Would you give them a few days of preventive treatment?

Dr Baroody: If you remove the foreign body and the ear looks perfectly healthy, there really is no need for that. If the external canal is abraded, and looks a little red, then I put a patient on about 5 or 6 days of a topical antibiotic just to make certain that the ear heals without otitis externa. But if the canal looks clean, and you pull the object without trauma, I don't think you need to treat them.

Dr Dohar: Another host factor is the anatomy and configuration of the ear canal. Some patients come in with repeated episodes of otitis externa, and there is nothing on the systemic checklist, no skin pathologies or behaviors. Sometimes the anatomy of the canal is just not self-cleaning. Either the canal has a very acute angle, or it's very small and it therefore tends to retain debris, and tends to be very moist and humid. I actually have them use blow dryers, if they can. I had one patient with six episodes of otitis externa in 4 months. I had the mother start blow-drying the ear canal after the child bathed, and it worked very well. Some of us use prophylactic drops after water exposure, as another means. Sometimes in older men, more hair in the ear canal can be a factor.

Dr Shulman: I have an anatomic question. My understanding is that in the adult, the inner two thirds of the external canal is bony, and the external one third is cartilaginous, and that in children, virtually the entire canal is cartilaginous. Presumably, the cartilage ossifies as one ages. Does this have any clinical importance?

Dr Dohar: That's an excellent question. When you do pneumatic otoscopy in a very young child whose canal is almost all cartilaginous, the whole thing tends to move. And you get the illusion of tympanic membrane movement. Also, some physicians rely very heavily on tympanometry to make the diagnosis of otitis media. If you do tympanometry in those very young children, you are always going to get a very classic Jerger type A tympanogram, whether the middle ear is full of pus or not. So this is a problem if you're using ancillary tests like tympanometry to diagnose otitis media. Otherwise, I don't imagine it predisposes to otitis externa. Frankly, I don't know that I've seen a case of otitis externa in a very young baby where the canal is still cartilaginous.

Dr Shulman: I was actually wondering whether it might protect against otitis externa.

Dr Guthrie: So, in the otherwise healthy host, one would not expect the presentation to be any different at different stages of life. The treatment would be the same. The lack of systemic signs would direct you toward an external otitis only. And it's mostly with older adults, like long-term diabetics, that you would become suspicious of other problems besides the traditional classic otitis. Should we move on to microbiology? Dr Roland will lead that discussion.

Dr Roland: Over the last three or four decades, there have been a fair number of studies that looked at the bacteriology of this disease. Interestingly enough, prior to World War II, it was universally regarded as a mycotic infection. That was just a truism that everybody believed in. It was only as a consequence of the exposure to humid environments experienced by servicemen in World War II that people started to examine it. The biggest single study was published in 1952 in Florida by David Singer, a microbiologist, and coworkers,[2] who looked at 646 individuals with external otitis, and compared them to almost 1,400 normal patients, in terms of culture.

As you all know, the external auditory canal is normally host to a variety of bacteria, mostly gram-positive diphtheroids, micrococci, and a lot of nonpathogenic staphylococcal species, such as *S epidermidis* and *S albus*.

There are some methodological considerations. Does one simply culture everybody that has external otitis, and assume that what you culture is the causative organism? Since the external auditory canal normally harbors a number of microbacteriological organisms, that could be a flawed methodology. Another way is to compare the microflora of infected people to that of noninfected people. And to compare the microflora at the time of infection to the microflora in the same person after the infection has resolved. This has shown some interesting things. For instance, during the time of infection, the incidence of micrococci, diphtheroids, and nonpathogenic staphylococcal species actually goes down, and it gets higher as the patient gets better. By comparing those studies, it's possible to sort out which organisms are pathogenic and which are not. As it turns out, most external otitis is caused by gram-negative organisms, principally *Pseudomonas*, with a substantial subportion of it being caused by *Staphylococcus aureus*, and a less substantial percentage caused by pathogenic streptococci.

If you look at the four studies[2-5] that I wrote the numbers down for, *Pseudomonas* accounts for somewhere between 50% and 65%. The other gram-negative organisms account for somewhere between 25% and 35%. Pathogenic *Staphylococcus* accounts for somewhere between 15% and 30%. And pathogenic streptococci between 9% and 15%. Interestingly enough, one can grow enterococci out of infected ears that aren't present in uninfected people. But they're almost never there as single pathogens. They're almost always associated with one of the other three or four major pathogens. So it's assumed that they are not really pathogenically very important. If you look at *Pseudomonas* in terms of phage and serotyping, there is no particular subspecies that seems to be predominant. It is not uncommon for there to be more than one *Pseudomonas* subspecies present. In some of the studies, based on phage and serotyping and colony characteristics, as many as four different types of *Pseudomonas* will be present in a given infection, suggesting that this really is an opportunistic infection, and that the *Pseudomonas* move into an empty niche, or that a niche has somehow changed and become more hospitable to them.

Water, of course, is an important etiologic agent, but it does not seem to be directly related in the sense that the water introduces the pathogenic bacteria. There is a famous study by Calderon and Mood,[6] who actually cultured almost 100 swimming pools, trying to recover the pathogenic organism from the pool in which their patients had swum; they were unable to do so in even a single case. The study by Agius et al[5] also looked at pools, but they were unable to recover *Pseudomonas* from any pool in their series of 48 patients. The etiologic factor that we haven't talked much about that seems to make this environment suddenly hospitable to *Pseudomonas* is the change in pH. Sayfield and Fraser[7] did pH studies on swimming pools, and in fact, discovered that the majority of their swimming pools that were associated with external otitises had an alkaline pH. And so, the evil that swimming appears to do is to alter the pH of the external auditory canal.

The altered pH then allows the pathogenic gram-negative organisms to begin to grow. There is a substantial minority of gram-negative rods other than *Pseudomonas*, principally, protease species, including *P vulgaris* and *P mirabilis*. And then a scattering of all sorts of other things, from *Herellea* to *Escherichia coli* and other pericolonic bacteria. As regards fungi, Singer et al[2] cultured almost 75 different species of fungi out of normal ears. They were actually more common in normal ears than in infected ears, with the exception of about 15%, from which you could culture either a form of *Candida*, or *Aspergil-*

lus. *Aspergillus niger, A fumigatus*, and several of the *Candida* species were cultured more commonly in sick ears than in healthy ears. But the list of saprophytic fungi that grow infrequently in ear canals is very long, and they probably have no pathologic significance.

Dr Guthrie: Are there any more recent data, concerned with changing bacterial flora because of aggressive antibiotic use?

Dr Roland: The study by Clark et al,[4] in 1997, essentially showed exactly the same thing that Singer's study showed in 1952.

Dr Shulman: It's reassuring to know that there's at least one infection in which the microbes haven't changed drastically over the last four or five decades.

Dr Dohar: There is a large study that was presented in May of 1996.[8] It was a multicenter trial, with a large number of patients enrolled. The conclusion is the same: there has been no real change in the bacteriology of otitis externa. Even more significant is the fact that there's been no change in the resistance patterns. These are, by and large, community-acquired infections in healthy hosts. But so are many other infections, like otitis media. Topical therapy is very nice, if you can use it. It doesn't appear to lead to resistance. We published a study in the *Archives of Otolaryngology*[9] on *Pseudomonas aeruginosa* in 1,003 children over a 5-year period that came to our outpatient department, from whom we were able to isolate *P aeruginosa* from ear drainage. A percentage of them had otitis externa, but a percentage also had middle ear infections. Over 5 years, we measured their resistances to several antibiotics. We found absolutely no change over the 5-year period. Polymyxin B sulfate was fabulous 5 years ago, and it's still fabulous now; 99.8% of those strains were sensitive. So, in cases where you can use topical therapy, even for middle ear infections that are presenting as drainage in patients who are otherwise not very ill (no high fever or great pain), we would do these patients a service to use topical therapy rather than systemic therapy.

Dr Guthrie: And the concern about fungal infection is not a significant issue?

Dr Roland: That's right. That's the big discovery of the 1950s.

Dr Dohar: In some cases I've had, the otorrhea persists in spite of daily suctioning of the ear canal, and I know they're complying with regard to their medications, but nonetheless, they're still not getting better. I culture them, and all I recover is fungus. And if I switch them over to Lotrimin drops, I've often had them dry up in 2 or 3 days. So would you agree that, maybe as an opportunist, the fungus may overgrow?

Dr Roland: I think as an opportunistic infection, in response to broad-spectrum topical antibiotics, you can get a secondary fungal infection. I usually find I can treat it very successfully with Domeboro.

Dr Shulman: I think that if the ear drops that you routinely use contain hydrocortisone and antibiotics, they can suppress the bacterial flora. One would expect that there would be unusual patients in whom fungus overgrowth would occur. But I think the fact that it's relatively unusual speaks to the fact that fungi are rarely important here, even though they commonly can be found in the mix.

Dr Guthrie: So, the primary pathogens remain the same mix of gram-negative and gram-positive organisms we've had with us for 40 years, and they have not forced treatment changes on us.

Dr Harris: Cases of external otitis in a normal host with an intact eardrum are the majority, obviously. But again, we do have children with chronic perforations or tympanostomy tubes that have chronic drainage. In some ways, they may or may not be easier to diagnose. They can go to the otolaryngologist's office, and be cleaned, and actually have the drainage cultured as it comes out of the perforation. Children who have been on multiple courses of systemic antibiotics may be at risk for acquiring resistant organisms. Bluestone's group has looked at large numbers of children with chronic suppurative otitis with tubes in place. And once again, *Pseudomonas* is at the top of the list. There have also been some questions raised about anaerobes by Dr Brook. We also need to be aware of fungal etiology in an abnormal host.

Dr Guthrie: But in the traditional primary care presentation, is there any reason for a culture or Gram's stain?

Dr Baroody: No. Again, the big issue is follow-up. If they get better after treatment, that's it. If not, then one performs a culture. One might perform a culture right away if there is a previous history of multiple problems with recurrent ear drainage, or a tube.

Dr Dohar: It seems that the most protective mechanism that the ear canal has against otitis externa is acidification. The acidifying agent that we naturally produce is cerumen. I have some patients who are aggressive at removing every bit of ear wax from the ear. We mentioned earlier that scratching the ear canal in removing wax is a problem, but it also removes the buffering system, which is important in activities like swimming. In "repeat offenders," I'll acidify the ear canal with VōSoL after the resolution of the infection until I see that they start making wax again, and then take them off the VōSoL.

Dr Roland: That's a critical issue. The importance of the acidity of cerumen is highlighted by the fact that a few years ago Driscoll et al[10] analyzed the cerumen from several hundred normal patients and found it to average pH 6.9, but from diabetic patients, in whom necrotizing external otitis occurs, it was close to 8. That appears to be the defect in diabetics that makes them vulnerable to osteomyelitis.

Dr Guthrie: Let me ask a question that typically comes up in primary care. You've got a 14-year-old competitive swimmer who's trying for the state championship. The child has recurrent infections, but is in the pool hours a day. What can you tell them? How can they avoid the infections, other than by not swimming, which is unacceptable? Are there treatments that they can use to change the pH?

Dr Bailey: What I've done is to have these patients use some sort of oil drops before they swim, and then a mixture of either vinegar and water, or alcohol and water, after they swim. And be meticulous about getting their ears dry. The blow dryer would be good for that.

Dr Guthrie: I recommend alcohol and vinegar, or the proprietary preparations like Domeboro or VōSoL.

Dr Harris: And remind the parents not to use the blow dryer on the hot setting.

Dr Roland: I know of an otologist who used to take the wax he removed from some patients, suspend it in mineral oil, sterilize it, and dispense it as a drop. It met with limited patient acceptance.

Dr Guthrie: I would think so.

Dr Shulman: I'd just like to come back to one of my favorite topics for a second, which is the streptococci that we mentioned. I think one needs to be cautious in terms of comparing microbiologic studies over the decades, because the names of the organisms have changed. For example, what are now called enterococci were all called streptococci initially. I think the enterococcus, which is isolated from the middle ear, is interesting, because enterococci are commonly isolated from a variety of anatomic sites as co-travelers from the gallbladder and other sites, for example, and don't generally require therapy unless they're from the bloodstream. So, no one should be focusing particularly on the enterococcus, which is a difficult organism to treat, and trying to treat it.

Dr Guthrie: To summarize. In the traditional presentation of pain, discharge, and lack of systemic symptoms in previously healthy hosts, there is no indication for lab work or culture. There is no indication for other than topical treatment at this point. The compromised host, either anatomically compromised because of chronic perforation or tubes, or a systemically immunocompromised host, requires considering cultures for unusual organisms. A response failure would lead you into looking for unusual things: mycotic infections, resistant situations, or other anatomic or pathologic problems. But in the traditional presentation, one goes ahead with clinical diagnosis and treatment.

Dr Witsell: I'd like to ask the panel if they've had any experience with otitis externa in patients with HIV, and if so, what kind of organisms are being detected?

Dr Harris: We see more otitis in the pediatric HIV population, which is a population that has a lot of otitis to begin with. We also see children with HIV come in with chronically draining ears. And it has been predominantly *Pseudomonas*. These are particularly difficult to treat if we feel we need systemic therapy, because of our limited armamentarium. Typically, these children do not require hospitalization, but they are not responding to topical therapy.

Dr Shulman: I'd like to make one other comment on microbiology. There are reports increasingly of methicillin-resistant *S aureus* strains being isolated in external otitis. There are reports of children with invasive staphylococcal infections, osteomyelitis, etc, that are community-acquired. And frequently, these are methicillin-resistant strains. I don't think they have reached the point of concern that's going to drive changes in management. But we need to be cognizant that there may be some subtle shifts occurring.

Dr Guthrie: Do you think those shifts are coming primarily because we're seeing a widespread change in that resistance pattern anyway?

Dr Harris: Yes. I think what's happening is that it's more clearly been reported in the adult, particularly the elderly, that community-acquired, methicillin-resistant *S aureus* is a problem. And that has to do with the epidemiology: residence in nursing homes, travel from the acute care facility, back to the nursing home, back to the acute care facility...It's become a big problem in long-term care facilities. And as the zones of contact become wider, the organism has become more predominant in the community. It warrants consideration.

Dr Dohar: I think we had 30 cases that presented to us, over about a year and a half's time, with methicillin-resistant *S aureus* isolated from ear drainage. We made two observations. First, they did not seem to differ a whole lot from routine cases. And because I have a research interest in this area, we tend to do more culturing as a routine than would generally be done. So, we found a lot of these after the fact. And the patients were often better, just from routine therapies. We postulated that this is because we use topical therapy for the treatment of almost all cases of otorrhea. And I think that even when the microbiologist's routine susceptibility panel shows resistance to systemic drugs, when you overwhelm these infections with the concentrations that you use topically, you get fairly good eradication. We did have a very interesting case of one child who had methicillin-resistant *S aureus* that kept recurring. She had six infections in a matter of 3 or 4 months. I actually took her to the operating room, and pretty much cultured everything: the nasopharynx, the nasal vestibule, the middle ear with a directed culture, and the external canal. I only found the resistant *S aureus* in the ear canal itself. So I patched the hole, and she's never drained again, nor has she developed an effusion again. I took one other recurring case to the operating room and cultured everything, and found it in the nasal vestibule, and treated it with Bactroban to the nasal vestibule. I did find some in the canal, although that was probably the drainage, and treated the canal with Bactroban. And again, the child got better. So these cases do happen, and they definitely warrant very careful attention.

Dr Shulman: This will probably be a slowly increasing problem, over the years.

Dr Dohar: As I said, we had a rash of these cases in our community, and these were in healthy children. They were not hospitalized, as far as we could tell.

Dr Harris: Were they in day care?

Dr Dohar: We asked questions about whether they had elderly grandparents or relatives in nursing homes. We were not able to find anything based on our questions to account for this. Some were in day care. But not an overwhelming number.

Dr Harris: But I think the other point that you were making is that the problem was not resolving, or it was recurrent, and that directed you then to look for something unusual.

Dr Guthrie: And without that, you wouldn't worry about it at initial presentation. You would treat them as we historically do.

Dr Dohar: That's right. And most of them will get better.

Dr Guthrie: Dr Shulman, from the pediatric perspective? Special considerations?

Dr Shulman: Well, I think we've touched on most of the unique aspects of otitis externa in children. I'd just like to review a couple of items. Malignant or necrotizing otitis externa is, relatively speaking, much less common in children than in elderly adults. And when it occurs, it is a problem associated with immunocompromised, particularly neutropenic, patients. An association relatively unique to pediatrics is Langerhans cell histiocytosis, which I've already discussed. And to emphasize just how unusual the unusual aspects of otitis externa are in children, I've done a Medline review of the last 5 years, and I've only come up with a couple of reports specifically related to pediatric otitis externa. Two of these are case reports. One is of a child whose acute lymphocytic leukemia presented as necrotizing otitis externa.[11] There's another report, from the Phoenix Children's Hospital, of otitis externa masquerading as mastoiditis.[12] There is an interesting report from Europe of 5 children with Langerhans cell histiocytosis who had refractory otitis externa.[13] These children were 6 months to 6 years of age and responded to topical 20% nitrogen mustard otic drops. I think that there are some other issues that are unique to pediatrics that relate to some of the newer therapies of otitis externa, namely, the quinolone class of agents. There is a raging controversy related to the safety of the quinolone agents in children. Animal studies in young dogs have shown arthropathy that develops as a consequence of quinolone usage.[14] Systemic usage, I should point out. Histologically, these young animals can be demonstrated to have pretty striking cartilage damage, with chondrocyte necrosis and blistering of the cartilage, particularly the large joints. On the other hand, there is a growing experience[15] in other countries in which systemic quinolones have been utilized for some years now, in children, without difficulty. For example, in Japan, since 1993, norfloxacin has been widely used systemically, with over a million prescriptions written for children with various infections. This includes about 100,000 children 4 years and younger. And careful surveillance has failed to demonstrate any cases of joint pain in these children consistent with the animal arthropathy. Other quinolones have been used in Switzerland and other European countries. There has been little if any experience to extend the animal findings into humans. Nevertheless, this is of continuing concern to the FDA, and to the American Academy of Pediatrics Committee on Infectious Diseases, which has currently undertaken reassessment of the status of quinolones in children. This has been stimulated by the fact that we need additional antibiotic agents to deal with some of the resistance not related to otitis externa, of course, but related to other kinds of infections, including otitis media, and other infections caused by *Streptococcus pneumoniae*, where we're having lots of resistance problems. We certainly could use some additional classes of drugs. But I would like to mention something that was published last week in *Infectious Diseases in Children*. After a review article on quinolones in children, the Editor, Dr Brunell,[16] wrote a very conservative few sentences that summarize much of the pediatric community's view on this. To paraphrase, he says until oral fluoroquinolones are approved for treatment of otitis media, it would be prudent not to use these drugs in children; that he would not like to have to defend you in court if a child for whom you had prescribed one of these drugs developed any joint complaints in the future; and that the widespread use of these drugs for otitis media would result in resistance to a class of drugs that is very useful for other indications, without appreciably increasing our armamentarium for treating otitis. Well, I'm not sure I agree with all of that, but it demonstrates the fact that the quinolones, with respect to pediatric usage, are not in a very positive circumstance at the moment, although this is being addressed at several levels.

Dr Guthrie: To clarify, you're talking about systemic quinolone use for otitis media.

Dr Shulman: That's correct. Or other respiratory tract infections. But topical usage, particularly in an area that's inflamed, is extraordinarily unlikely to lead to significant amounts of systemic absorption. And therefore, it would be quite unlikely that one would see any kind of systemic consequences from that kind of topical usage.

Dr Baroody: What is the experience of using them in children with cystic fibrosis?

Dr Shulman: Dr Schaad and others[17] in Switzerland have looked at cystic fibrosis children who have had repeated courses of quinolones, usually 2 or 3 weeks at a time, multiple times over some years. Some of those cystic fibrosis patients have ultimately died of their primary disease, and examination of cartilage has not demonstrated signs of toxicity. And that's been taken to suggest that we're not likely to see, in humans, the same kind of chondrocyte problems that have been reported in the young animals. This has prompted a reassessment in the United States, asking whether we as a society have taken much too restrictive a view of the safety issue, and put too much credence in the dog studies.

Dr Harris: There has been a cystic fibrosis experience in the United States, as well. And they have not found any issues regarding arthropathy. The problem is that the numbers are small. People have used oral fluoroquinolones on a compassionate use basis when there have been extenuating circumstances. If that is done, it's a nonapproved use of a drug. And therefore, we do recommend getting written consent from the parents before prescribing this drug.

Dr Dohar: The FDA has recently visited the issue of fluoroquinolones used systemically in children. As I understand it, there was a large review of several thousand children from the United States. And in the cystic fibrosis patients, at least if I understood the data correctly, it wasn't so much that there was no joint arthropathy found in the postmortem studies — and some of the data was magnetic resonance imaging of the joints — but that the incidence was no different between the children who had exposure to fluoroquinolones and those who did not. The confounding variable is that children with cystic fibrosis may have joint arthropathy as part of the disease, so sorting that out is problematic. Unfortunately, most of the compassionate use experience in this country has been in this population of patients. So it's less clear than in some of the European and Asian studies. Regarding the issue of topicals that was brought up, I would say that there is just no evidence to support that caution. There is absolutely no reason to believe that resistance is a problem with topically used agents, provided that you have efficient delivery. Our ear experience echoes the same thing. We have not seen resistance develop to Cortisporin, which has been around since the 1970s; therefore, efficient delivery is presumed. Now, where I have seen problems is in cystic fibrosis patients, with topical use of antibiotics in the sinuses and lungs. But one has to question the effectiveness of topical delivery medications to the sinuses and lower, more distal airways. I think that's the key. Also, in non–cystic fibrosis patients, there are a couple of series in the literature on topical use of antibiotics in sinusitis, where resistance has developed. But again, I think delivery is the issue. So I think it's safe to say, based on all that we know, that you probably can use drugs like ciprofloxacin topically in the ear without the concern that you will obviate that as a choice for yourself systemically down the road if you need it.

Dr Guthrie: Because you can overwhelm the infection with the heavy concentrations.

Dr Dohar: Right. That's the theory as to why resistance doesn't develop. It hasn't been proved.

Dr Guthrie: Now, I get to talk about the primary care perspective. The presentation of otitis externa is regarded in most situations, by a primary care physician, as a relatively common, particularly seasonal disorder, and a mundane thing. This is not a life-threatening presentation. The key issue is to make the right diagnosis clinically. What I worry about when I see a canal full of exudative material is, is it strictly external, or is there any reason to think that this is a ruptured otitis media, which may require systemic antibiotics? The history can give you a good guide on that. Treatment is traditionally empiric: polymyxin, neomycin, hydrocortisone, Cortisporin. I'm a great one for rechecking people, but in a healthy traditional presentation — first time, not a recurrence — I would not tell them to come back. I would tell them to come back only if they had a problem. If you were trying to delineate something else, you would request them to come back. Any comments?

Dr Weis: I think there is a misperception in primary care that otitis externa is just otitis media outside the eardrum. I don't think people understand the microbiology of it. They think that the organisms that cause middle ear infections are the same ones that cause ear canal infections. So I don't think they realize that this is mostly a gram-negative issue, a *Pseudomonas* issue in general. And that's why I'm excited about these new ear drops we're talking about today.

Dr Guthrie: So when do we send an external otitis patient off for consultation? For failure to resolve, or concern over the accuracy of the diagnosis. Failure to respond to traditional treatment, after at least one, or even two courses.

Dr Witsell: Clearly a good 20% of the patients that are referred to me from primary care for failure of treatment of otitis externa are there because they're given inappropriate therapy, that is, systemic antibiotic therapy with no topical agent at all. So, one place we can make an impact is to teach what is the mainstay of therapy for otitis externa.

Dr Shulman: I think that reflects exactly what Dr Weis indicated, in that there is confusion among many primary care physicians that the same kind of organisms that cause media are causing externa. So, they're using systemic therapy that's going to be inappropriate for externa.

Dr Guthrie: You won't get a concentration in the external ear canal on systemic therapy. And, too, it will be for a completely different spectrum.

Dr Baroody: One of the important points is whether the drops can penetrate. The child might need a wick. Are primary care physicians putting wicks in external auditory canals, or do they refer these patients?

Dr Weis: I believe the farther you get from a large city, the more they do it. Because of the inconvenience of seeing a specialist, the primary care physician is expected to do more. But in a metropolitan area, or fairly close to it, most of those people are probably not using wicks.

Dr Guthrie: Training is different across the nation. It's very regional in nature. And most of us are not trained in using wicks.

Dr Bailey: I think this is an important area, and it points out that we're not seeing exactly the same population of patients. The reason it's mundane for the primary care physician is that 98% or 99% of the people get well. The people we see have either had inappropriate treatment, or they haven't had the ear cleaned out, so that the medicine can get in, or a wick put in. And it is an area that we need to address, for education of the primary care physician.

Dr Guthrie: That's a very good point. Most of us would not know how to clean the ear out without causing undue pain. And I certainly don't know how to wick it. These things should be included in training of the primary care physician.

Now to discuss treatment guidelines. Do we have them? Do we need them? And if we develop them, how do we communicate them? For external otitis, I'm not aware of any treatment guidelines. Is anybody aware of any?

Dr Baroody: I don't think so. But I think they need to exist, primarily to try to reduce the use of systemic antibiotics when not necessary, and to identify, if possible, criteria for the use of systemic antibiotics when they are appropriate. If we can establish that, it would be pretty helpful.

Dr Weis: It would be nice to have them for lots of reasons. For example, in Kentucky a large percentage of the children we see are on the medical welfare system known as Medicaid in Kentucky. This program has a significant number of formulary restrictions, including ear drop restrictions. My understanding is that the system only covers one ear drop for otitis externa, and all of the noncovered ones are quite expensive, which basically eliminates them for the welfare population. Treatment guidelines could be used to stimulate such Formulary Boards to be open to other options. My feeling is that ciprofloxacin otic with or without hydrocortisone is a fine therapeutic option, but I don't think we could get it paid for by our Medicaid program without the drops' having been approved by the Formulary Board. It eliminates a good therapeutic option for us. But if we had accepted guidelines to take to the Board, we could say that this treatment is considered the standard of care; that this is what is being used nationally. That would certainly assist us in our efforts to give these patients the best care.

Dr Guthrie: What does one have to do to develop guidelines?

Dr Witsell: Guidelines typically start out with expert opinion. A panel like this, which comes up with an idea as to a reasonable standard of care. One of the problems that we've seen in the past, especially with other treatment guidelines, is that they don't go on to be tested and linked to outcomes. I would hope that this panel, if its members come up with treatment guidelines, would undertake the additional responsibility to follow the outcomes associated with the guidelines.

Dr Guthrie: There are two separate things here. We can make our own recommendations of what seems to be a logical, clinically sound pattern, which we as a panel can recommend to the practice community, to take into the official guidelines.

Dr Harris: An organization has to sponsor the development of the guidelines. Then multiple organizations have to be participants, and then it has to go back to the individual organizations, be approved by their boards, and disseminated into the official journals of those particular organizations. It is a cumbersome process. But if you don't have outcome measures linked to the guidelines, you have no way of knowing whether these are successful or not, or whether they're even followed.

Dr Shulman: Probably, the development of such guidelines should be through the appropriate academies. Either the American Academy of Pediatrics or the American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc, would certainly be most appropriate.

Dr Harris: And the Academy of Family Practice.

Dr Guthrie: Yes, they would logically be involved. I would propose that we suggest a logical treatment pattern for primary care physicians. And then if anybody has the desire to go forward with this, we can negotiate that question later, because we can each go to our respective academies and see if there is any interest in supporting this. I think there's a huge need. From what you're saying, Dr Witsell, 20% of your referrals are given systemic therapy when there's easy-to-use topical therapy, which is highly successful, most of the time. I think when you're comfortable that it's an uncomplicated otitis externa, then initial treatment would be with a topical antibiotic or antibiotic-cortisone mixed topical drops. If that's unsuccessful, either repeating the course or switching to a different topical preparation would be the second step. The third step would involve, I think, referral.

Dr Roland: One problem is that patients perceive that topical therapy is weak, and systemic therapy is strong, so they're very happy to get a nice antibiotic prescription. And they're suspicious when some doctor wants to switch them to just a drop.

Dr Dohar: Yes. The same is true of acute otitis media that presents as otorrhea through a tube. The microbiology is very different in that scenario. And some recent studies have shown that you don't really need systemic agents in the majority of those patients. But most often, when you look at children who are treated by primary care physicians, they are treated with systemic agents alone, or in a minority of cases, systemic plus topical. But rarely topical alone.

I've been told by a lot of my community family practitioners that they were instructed in their residencies never, ever to use ear drops if there's even a chance that the eardrum has a perforation. Many of my pediatrics colleagues have echoed that as well. And we've been aggressive in our community to try to reassure people that this is, in fact, the standard of care, and okay in an inflamed ear.

Dr Guthrie: Of course, it's a contraindication on the label.

Dr Harris: Yes. The ototoxicity of aminoglycosides is the issue.

Dr Dohar: The PDR has softened what they originally said. Now they say "use with caution" for agents like Cortisporin. But you're right, it's an admonition.

Dr Guthrie: The primary care doctor's only source of information on the risk of peripheral neuropathy is the PDR, that is, the package label.

Dr Dohar: Well, it's approved use is for otitis externa. But there has been such fear instilled in people regarding the possibility of eardrum perforations. And it gets back to distinguishing between otitis media and otitis externa.

Dr Guthrie: Just for the record, is neomycin toxic in this preparation?

Dr Roland: It's very ototoxic. Ironically, it is much more ototoxic than Tobradex or tobramycin, or gentamicin.

Dr Dohar: There were some lawsuits that had sprung up around the country alleging hearing loss secondary to drop use. And so Lundy and Graham published an article[18] that was the result of a questionnaire that clearly stated that it is considered standard-of-care to use drops, even in the face of a nonintact eardrum. Lundy and Graham[18] went on to say that the risks of hearing loss of otitis media are as great or greater than the risks of ototoxicity from topical preparations. The article did not say there was no risk in using these agents. Some people misinterpreted the language to say that. But they did clearly say that there is little risk, and that it's certainly less than if you don't treat them appropriately.

Dr Guthrie: Would the topical quinolone be reassuring in that situation, where you would not have that risk?

Dr Bailey: Absolutely.

Dr Roland: It's really ironic to otolaryngologists, because as soon as the quinolones came out, otolaryngologists assumed that there would soon be a topical otic drop made of quinolone, because it's such a logical thing. We've been waiting year after year. And all of the articles have said as soon as the quinolone drop is out, then we're going to discard the other drugs, and it's just never come about.

Dr Witsell: In my residency training program, we used Cipro ophthalmic solution, commonly.

Dr Baroody: People use it now.

Dr Guthrie: All right. Do we use 10 days of therapy? Four to eight? Six?

Dr Shulman: I think the 10 days all derives from strep throat.

Dr Harris: It takes a minimum of 9 days, almost 10 days, to eradicate the strep organism and prevent rheumatic fever. That was established in the 1940s.

Dr Shulman: So the 10 days is derivative of a circumstance where we do know the appropriate duration of therapy. But in this situation, we don't really have good evidence, I think.

Dr Bailey: One of the things that's interesting and important in treating otitis externa is to keep the treatment going for several days beyond the time that the symptoms resolve. As we pointed out, many of these patients are seen once. And if they feel better, they may not comply with a follow-up appointment. So it seems to me that a treatment recommendation needs to be for at least 3 days beyond the cessation of symptoms.

Dr Guthrie: Do you think that's a good recommendation, 3 days beyond the cessation of symptoms?

Dr Roland: There is some evidence for sinusitis that it takes 7 days to eradicate the bacteria. And so that's the basis of the 10-day recommendation, to give you a couple of days' margin. But I don't think there is any bacteriologic or microbiologic data for this disease.

Dr Guthrie: What about hydrocortisone?

Dr Dohar: Among otolaryngologists, it's a widely held prejudice that it's important to the treatment of the disease. And that is, I think, one reason why you see that a drop with substantial ototoxicity has a higher market share than a drop with no ototoxicity. It's because the drop with the ototoxicity has hydrocortisone mixed in with it. But there are no data.

Dr Shulman: I think the clinical trial that was included in the information that we were sent by Bayer Corporation before this Roundtable convened specifically pointed out, nicely, that there is an added benefit in terms of shorter duration of pain, and faster resolution of symptoms if one has hydrocortisone included in the preparation.

Dr Weis: Many family physicians fear hydrocortisone, because they're worried they're going to cause fungal overgrowth.

Dr Shulman: It seems to me that the presence of hydrocortisone seems to be a benefit without a particular downside.

Dr Roland: Neomycin is highly sensitizing, and somewhere between 5% and 15% of people will have an obvious clinical allergic reaction to topically applied neomycin. If you look at patch testing, the incidence of hypersensitivity is as high as 30%. Many patients who have resistant otitis externa don't, in fact, have a microbiologic disorder, but a low-grade hypersensitivity to the neomycin. The package insert itself acknowledges that failure to resolve may be nothing more than a manifestation of hypersensitivity. And so those patients continue to drain, even though bacteriology is not the problem; they're just hypersensitive to the medication, and they get more and more medication. And at that point the fungal superinfections occur, and they've been on therapy for 3 or 4 weeks. I think once we eliminate neomycin from treatment of this disease, some of these problems are going to take care of themselves.

Dr Dohar: There have been several studies, some in the dermatology literature, and some in our own,[19] in which the steroid was actually a sensitizer. You treat inflammation with topical steroid, so you wouldn't think that inflammation would be caused by topical steroid. But in fact, that does occur. And it occurs in ear preparations as well as in topical skin preparations. The numbers are higher for the studies that used patch testing as their end outcome measure, as opposed to those that measured clinically significant allergic response.

Dr Roland: In rodents, hydrocortisone is fairly inflammatory to the middle ear mucosa simply as sort of a chemical irritant, initially.

Dr Dohar: There has also been some question raised about possible inner ear toxicity associated with steroid preparations when applied to the middle ear. That may be another risk. But those are all minor things.

Dr Guthrie: I have available the market share data of otic preparations, provided by Bayer Corporation.[20] If you look at it in regard to prescriptions, rather than dollars, neomycin, polymyxin, hydrocortisone has 71% of the ear drop market. Cortisporin has 4%. Otocort is 6%. Pediotic is 3%. Here are the company data on patient ages for otitis externa diagnosis. You can see the domination by ages 3 through 59.

Dr Shulman: I think it's impressive that 16% or 17% are people over 65.[20] That's an impressive number.

Dr Guthrie: It spreads across the age groups. Fifty percent would be 18 and over. As to who treats external otitis, 72% of patients are seen by primary care physicians, and 28% are seen by otolaryngologists.[20] Now we're going to talk about the pivotal study for the marketing of the ciprofloxacin otic, which is actually going to be ciprofloxacin hydrocortisone suspension. What you have here is a three-arm study (see Tables, pages 19-23). The otic solution, 0.2% of ciprofloxacin versus 0.2% suspension, including hydrocortisone, was studied versus polymyxin, neomycin, hydrocortisone otic suspension for acute diffuse bacterial otitis externa. Also to compare the efficacy and safety of the Cipro otic drops, with or without hydrocortisone. Also polymyxin, neomycin, hydrocortisone for the treatment of acute diffuse bacterial otitis externa, and to determine the time to end of ear pain for each antimicrobial treatment. That — the time to end of ear pain — is the the unique feature of this study. That was developed to determine if there's a difference between the plain ciprofloxacin solution and the hydrocortisone-included suspension. It's a prospective randomized nonblinded three-arm multicenter trial, on 842 patients around the United States. So, it's a large study. The study regimens were ciprofloxacin solution versus ciprofloxacin and hydrocortisone suspension, each administered as 3 drops BID, or polymyxin, neomycin, hydrocortisone given as 9 to 12 drops TID. All study drugs were in the deep portion of the ear for 7 days. So, these data will be on a 7-day treatment. And no concomitant systemic antibiotic use or topical agent. The end points were clinical response at end of therapy, and time to end of ear pain. Secondary parameters were bacteriological response. Here are your resolution characteristics: resolution plus improvement, 93% in the solution, 90% in the suspension with hydrocortisone, and 88% in the polymyxin, with failures, of course, being reflective of that. No statistical difference.

Dr Dohar: The other data I've reviewed recently for otitis externa have shown the same trend. Not only do adults take longer to get better, but the failure rate is typically worse in adults than children. We attributed it to a couple of things. First, when we looked at the adult data in another study, they actually were broken down by males and females. Adult males did worse than adult females.

Dr Guthrie: Compliance is probably a factor there.

Dr Dohar: In children, it tends to be a caregiver that puts the drops in, as opposed to self-administration. So, we thought it might be easier for somebody to put drops in somebody else's ear and then pump the tragus to get them down. But as to the second issue, between adult men and women: other than compliance, it might simply be that adult men have more hair in their ear canal, which may serve as an impediment to the drop delivery. And also, on average, their skin is thicker. Another factor is tissue penetration. I believe a young child has much less keratinized tissue there than do adults.

Dr Guthrie: So, the conclusions were that both of the drops, with or without hydrocortisone, were as effective as polymyxin-neomycin in the treatment. The addition of hydrocortisone to Cipro resulted in a statistically significant reduction in time to end of ear pain, when compared to Cipro solution alone. And both were well tolerated and safe when used as a 1-week treatment regimen. The last question for you all as experts is, how about the new drops? Are they going to be reserved for treatment failures? Are they going to compete for primary treatment in the new market? The BID dosing is a huge help. It avoids having to send it to school, get the school nurse to put it in, etc. And this is a final comment, because of the concern over Cipro absorption. They did not detect levels of Cipro absorption at all. And the concentrations of hydrocortisone could not be differentiated from endogenous cortisol. So there appears to be no indication of absorption across those surfaces. So it remains a topical product, as one would expect. Would the panel recommend to the company that they actively take these drops to the market?

General agreement of panelists.

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THE FOLLOWING ARE BRAND NAME PRODUCTS REFERRED TO IN THIS SUPPLEMENT.
GENERIC EQUIVALENTS ARE LISTED IN PARENTHESES.

Bactroban® Nasal (mupirocin calcium ointment, 2%)

Ciloxan® Ophthalmic Solution (ciprofloxacin hydrochloride)

CIPRO® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension)

Cortisporin® Ophthalmic Suspension Sterile (neomycin and polymyxin B sulfates and hydrocortisone ophthalmic suspension, USP)

Lotrimin® Topical Solution, USP 1% (clotrimazole topical solution, USP 1%)

Otic Domeboro® Solution (acetic acid 2% in aqueous aluminum acetate otic solution)

Otocort® (No longer available.)

Pediotic® Suspension Sterile (neomycin and polymyxin B sulfates and hydrocortisone otic suspension, USP)

Tobradex® (tobramycin and dexamethasone ophthalmic suspension and ointment)

VoSoL® Otic Solution (acetic acid otic solution, USP)

Ciprofloxacin (CIP) Otic Solution (SOLN, 0.2%) vs. CIP/Hydrocortisone Suspension (CIP/HC SUSP, 0.2%), vs. Polymyxin B-Neomycin-Hydrocortisone (PNH) Otic Susp for Treatment of Acute Diffuse Bacterial Otitis Externa

STUDY OBJECTIVES

- To compare the efficacy and safety of CIP otic drops, with or without hydrocortisone, to PNH for the treatment of acute diffuse bacterial otitis externa
- To determine the time-to-end of ear pain for each antimicrobial treatment

STUDY DESIGN

- A prospective, randomized, non-blinded, three-arm multicenter trial
- 842 patients from 30 U.S. centers were enrolled
- Study drug regimens: CIP Soln (0.2%) or CIP/HC Susp (0.2%), each administered as three drops BID, or PNH given as 9-12 drops TID. All study drugs were given in the deep portion of the ear for 7 days

INCLUSION CRITERIA

- Male or female outpatients ≥ 2 years of age
- Primary diagnosis of acute diffuse bacterial otitis externa of ≤ 3 weeks duration
- Clinical signs and symptoms of externa otitis within 2 days of study entry, including;
  - edema of the external auditory canal
  - tenderness with movement of the pinna, and
  - otalgia

EXCLUSION CRITERIA

- Acute otitis media
- Invasive malignant chronic otitis externa
- Dermatitis in the area of the affected ear
- Recent diagnosis and treatment of otitis externa
- Perforated tympanic membrane
- Known fungal infection of the ear
- Furuncles
- Mastoiditis
- Stenosis
- Exostosis
- Tumors of the ear
- Significant underlying disease
- Allergy to carboxyquinolones or PNH components
- Pregnant or breast-feeding women
- Administration of another investigational drug within 30 days of enrollment
- Previous enrollment in this study

These tables are modified from NDA 20-805.

VALIDITY CRITERIA

- Clinical diagnosis of acute diffuse bacterial external otitis
- Clinical response evaluated at end of therapy
- Study drug received for full 7 days, unless a treatment failure
- No concomitant systemic antibiotic use or topical agent in the affected ear or analgesics with anti-inflammatory properties

ENDPOINTS

- Primary Efficacy parameters: clinical response at end-of-therapy and time-to-end of ear pain
- Secondary Efficacy parameters: bacteriologic response at end-of-therapy

RESULTS: PATIENT ENROLLMENT

	CIP SOLN	CIP/HC SUSP	PHN	TOTAL
Intent-to-treat population	285	282	275	842
Efficacy-valid population for clinical response	246	244	238	728
Efficacy-valid-population for bacteriologic response*	153	146	146	445

* patients with documented pre-therapy bacterial pathogen

RESULTS: REASONS FOR INVALIDITY

	CIP SOLN	CIP/HC SUSP	PHN	TOTAL
Inclusion/exclusion violation	16	19	14	49
Noncompliance	15	8	14	37
Lost to follow-up	3	7	2	12
Study protocol improperly followed	4	2	5	11
Noncompliance with the study diary	0	2	1	3
Inadequate duration of therapy	1	0	1	2
Total	39	38	37	114

*RESULTS: DEMOGRAPHICS AND BASELINE MEDICAL CHARACTERISTICS OF EFFICACY-VALID POPULATION**

Variable	**CIP SOLN (n=246)**	**CIP/HC SUSP (n=244)**	**PNH (n=238)**
Age, years			
Mean ± SD	24.3 ±18.5	23.6 ± 17.4	24.2 ± 17.7
Range	3-83	2-85	2-83
Sex, n (%) female	125 (51)	130 (53)	115 (48)
Race, n (%) Caucasian	228 (93)	224 (92)	219 (92)
Unilateral infections, n (%)	209 (85)	206 (84)	213 (90)
Water contact within 4 weeks, n (%)	201 (82)	202 (83)	196 (82)
Duration of symptoms of current infection, days			
Mean ± SD	4.8 ± 4.1	4.3 ± 3.9	4.6 ± 4.2
Range	1-21	1-20	1-20
No episodes in last 12 mo, n (%)	199 (81)	204 (84)	203 (85)

* there were no statistically significant differences between treatment groups for any variable

RESULTS: CLINICAL RESPONSE FOR THE EFFICACY-VALID POPULATION

Time of Evaluation	**Response**	**CIP SOLN n (%)**	**CIP/HC SUSP n (%)**	**PNH n (%)**
End of Therapy	Resolution + Improvement	225 (93)	218 (90)	208 (88)
	Failure	17 (7)	23 (10)	29 (12)
14-28 day Follow-up	Resolution	205 (97)	201 (98)	185 (96)
	Relapse	7 (3)	4 (2)	8 (4)

RESULTS: CLINICAL RESPONSE BY AGE GROUP AT THE END OF THERAPY

Age	**Response**	**CIP SOLN n (%)**	**CIP/HC SUSP n (%)**	**PNH n (%)**
2-6 years	Resolution + Improvement	27 (96.5)	22 (100)	29 (100)
	Failure	1 (3.5)	0	0
7-12 years	Resolution + Improvement	64 (94)	75 (96)	52 (95)
	Failure	4 (6)	3 (4)	3 (5)
13-16 years	Resolution + Improvement	26 (96)	19 (90.5)	32 (91)
	Failure	1 (4)	2 (9.5)	3 (9)
≥ 17 years	Resolution + Improvement	108 (91)	102 (85)	95 (80.5)
	Failure	11 (9)	18 (15)	23 (19.5)

P24,785

RESULTS: BACTERIOLOGIC RESPONSE FOR THE EFFICACY-VALID POPULATION

Time of Evaluation	Response	CIP SOLN n (%)	CIP/HC SUSP n (%)	PNH n (%)
End of Therapy	Eradication/ Presumed Eradication	142 (93)	139 (95)	129 (88)
	Superinfection	8 (5)	4 (3)	4 (3)
	Persistence	3 (2)	3 (2)	13 (9)
14-28 day Follow-up	Continued Eradication	44 (94)	52 (95)	47 (96)
	Relapse	1 (2)	2 (3)	1 (2)
	Reinfection	2 (4)	1 (2)	1 (2)

RESULTS: BACTERIOLOGIC ERADICATION BY ORGANISM AT THE END OF THERAPY*

Organism	CIP SOLN n (%)	CIP/HC SUSP n (5)	PNH n (%)
P. aeruginosa	143 (99)	132 (99)	125 (92)
Pseudomonas species	6 (100)	2 (100)	5 (100)
S. maltophilia	6 (86)	5 (100)	8 (100)
Enterobacter species	8 (100)	8 (100)	11 (92)
Acinetobacter species	7 (100)	10 (100)	7 (88)
Klebsiella species	4 (100)	9 (100)	6 (100)
Miscellaneous gram-negative bacilli/cocci	23 (100)	16 (100)	15 (94)
S. Aureus	13 (100)	16 (94)	12 (100)
Streptococcus species	2 (100)	1 (100)	1 (100)
Total	212 (99)	199 (99)	190 (93)

* number of organisms eradicated plus presumed eradicated

TIME-TO-END OF EAR PAIN

- Estimated median time-to-end of ear pain:

CIP SOLN	4.6 days
CIP/HC SUSP	3.8 days (P=0.036 CIP SOLN vs. CIP/HC SUSP)
PNH	4.1 days

- Percentage who took analgesics was similar across the three treatment groups:

CIP SOLN	50%
CIP/HC SUSP	51%
PNH	53%

- Older patients appeared to have a longer time-to-end of ear pain (P<0.01)

SAFETY ANALYSIS

- Among 842 intent-to-treat patients, at least one treatment-emergent event occurred in:

CIP SOLN	66 (23%)
CIP/HC SUSP	70 (25%)
PNH	55 (20%)

- Headache, ear pain and pruritus were the most common events reported in all three treatment groups
- Premature discontinuation due to an adverse event occurred in 8 patients:

CIP SOLN	n = 1
CIP/HC SUSP	n = 4
PNH	n = 3

CONCLUSIONS

- CIP otic drops, with or without hydrocortisone, were as effective as PNH in the treatment of acute diffuse bacterial otitis externa
- The addition of hydrocortisone to CIP resulted in a statistically significant reduction in time-to-end of ear pain, when compared to CIP alone
- CIP SOLN and CIP/HC SUSP were well-tolerated and safe when used as a one week treatment regimen

CIPRO® HC OTIC

(ciprofloxacin hydrochloride and hydrocortisone otic suspension)

DESCRIPTION

CIPRO® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) contains the synthetic broad spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, hydrocortisone, in a preserved, nonsterile suspension for otic use. Each mL of CIPRO HC OTIC contains ciprofloxacin hydrochloride (equivalent to 2 mg ciprofloxacin), 10 mg hydrocortisone, and 9 mg benzyl alcohol as a preservative. The inactive ingredients are polyvinyl alcohol, sodium chloride, sodium acetate, glacial acetic acid, phospholipon 90HB (modified lecithin), polysorbate, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

Ciprofloxacin, a fluoroquinolone, is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows:

Hydrocortisone, pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-(11β)-, is an anti-inflammatory corticosteroid. Its empirical formula is $C_{21}H_{30}O_5$.

CLINICAL PHARMACOLOGY

The plasma concentrations of ciprofloxacin were not measured following three drops of otic suspension administration because the systemic exposure to ciprofloxacin is expected to be below the limit of quantitation of the assay (0.05 µg/mL).

Similarly, the predicted C_{max} of hydrocortisone is within the range of endogenous hydrocortisone concentration (0-150 ng/mL), and therefore can not be differentiated from the endogenous cortisol.

Preclinical studies have shown that CIPRO HC OTIC was not toxic to the guinea pig cochlea when administered intratympanically twice daily for 30 days and was only weakly irritating to rabbit skin upon repeated exposure.

Hydrocortisone has been added to aid in the resolution of the inflammatory response accompanying bacterial infection.

Microbiology

Ciprofloxacin has in vitro activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of ciprofloxacin results from interference with the enzyme, DNA gyrase, which is needed for the synthesis of bacterial DNA. Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections of acute otitis externa as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganism

Staphylococcus aureus

Aerobic gram-negative microorganisms

Proteus mirabilis
Pseudomonas aeruginosa

INDICATIONS AND USAGE

CIPRO HC OTIC is indicated for the treatment of acute otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of Pseudomonas aeruginosa, Staphylococcus aureus, and Proteus mirabilis.

CONTRAINDICATIONS

CIPRO HC OTIC is contraindicated in persons with a history of hypersensitivity to hydrocortisone, ciprofloxacin or any member of the quinolone class of antimicrobial agents. This nonsterile product should not be used if the tympanic membrane is perforated. Use of this product is contraindicated in viral infections of the external canal including varicella and herpes simplex infections.

WARNINGS

NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.

CIPRO HC OTIC should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

PRECAUTIONS

GENERAL: As with other antibiotic preparations, use of this product may result in overgrowth of nonsusceptible organisms, including fungi. If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment.

Information for Patients:

If rash or allergic reaction occurs, discontinue use immediately and contact your physician.

Do not use in the eyes.

Avoid contaminating the dropper with material from the ear, fingers, or other sources.

Protect from light.

Shake well immediately before using.

Discard unused portion after therapy is completed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 in vivo test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of CIPRO® HC OTIC suspension have been performed to evaluate carcinogenic potential.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 1000 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with CIPRO HC OTIC twice per day.

Long term studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical hydrocortisone. Mutagenicity studies with hydrocortisone were negative.

Pregnancy: Teratogenic Effects. Pregnancy Category C:

Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Animal reproduction studies have not been conducted with CIPRO HC OTIC. No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when CIPRO HC OTIC is used by a pregnant woman.

Nursing Mothers: Ciprofloxacin is excreted in human milk with systemic use. It is not known whether ciprofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: The safety and efficacy of CIPRO HC OTIC have been established in pediatric patients 2 years and older (131 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 2 years, there are no known safety concerns or differences in the disease process in this population which would preclude use of this product in patients one year and older. See **DOSAGE AND ADMINISTRATION.**

ADVERSE REACTIONS

In Phase 3 clinical trials, a total of 564 patients were treated with CIPRO HC OTIC. Adverse events with at least remote relationship to treatment included headache (1.2%) and pruritus (0.4%). The following treatment-related adverse events were each reported in a single patient: migraine, hypesthesia, paresthesia, fungal dermatitis, cough, rash, urticaria, and alopecia.

DOSAGE AND ADMINISTRATION

SHAKE WELL IMMEDIATELY BEFORE USING.

For children (age 1 year and older) and adults, 3 drops of the suspension should be instilled into the affected ear twice daily for seven days. The suspension should be warmed by holding the bottle in the hand for 1-2 minutes to avoid the dizziness which may result from the instillation of a cold solution into the ear canal. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 30-60 seconds to facilitate penetration of the drops into the ear. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

HOW SUPPLIED

CIPRO HC OTIC is supplied as a white to off-white opaque suspension in a 10 mL bottle with a dropper dispenser.

NDC 0065-8531-10

Store below 77° F (25° C). Avoid freezing. Protect from light.

CIPRO® is a registered trademark of Bayer AG.

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U.S. Pat. Pending.

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NEUROTRANSMITTERS AND NEUROMODULATORS INVOLVED IN LARYNGEAL INNERVATION

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BRAIN STEM NEURAL MECHANISMS FOR VOCALIZATION IN DECEREBRATE CATS

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OF OTOLOGY,
RHINOLOGY &
LARYNGOLOGY

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PREFACE

The contributions to this supplement are based on presentations delivered at the symposium "Some Recent Advances in Neurolaryngology" on May 23-25, 1996, during the 97th Annual Meeting of The Oto-Rhino-Laryngological Society of Japan, held in Fukuoka, Japan.

The symposium aimed at presenting the most recent progress in the field of neurolaryngology. The term "neurolaryngology," which entails the basic and clinical study of the neural control mechanisms of the larynx, has been used on many occasions, and recent progress in this field is prominent. We had the honor of organizing the symposium and choosing the topics and speakers.

In humans, there are 4 basic laryngeal functions: airway protection, which is particularly important during deglutition; effective glottic closure for fixation of the trunk while moving the upper extremities; airway opening for respiration; and phonation. For all of these functions of the larynx, the neural control mechanism is essential. Much research has been accumulated in the past to clarify the complicated mechanisms, but there are still many unsolved questions regarding the neural control of the larynx. In particular, little has been explored of the central mechanism of reflex, as well as volitional and autonomic, control of the larynx. These important topics are addressed in the papers printed here.

Each contribution deals with the authors' original work, together with a brief review of relevant literature. Each paper brings to light answers for many problems and conflicting views in the field. Nevertheless, many unresolved problems remain regarding the neural mechanisms of the larynx. At present, several subjects in neurolaryngology can be focused on as current topics, for example, in the central nervous system (CNS), 1) a more distinct neuronal pathway for vocalization, deglutition, and the laryngeal reflex arc, 2) the mechanism of auditory and other sensory feedback systems, and 3) explication of the programming and presetting for phonation and swallowing; in the peripheral nervous system (PNS), 1) functional and morphological considerations of neuromuscular junctions and proprioceptors and 2) endogenous innervation; and in both the CNS and PNS, 1) inquiry into nerve conduction and neurotransmission, 2) understanding the contribution of the autonomic nervous system, and 3) the process of development and repair following nerve injury, ie, degeneration, regeneration, and plasticity.

Some of these questions were clarified in this symposium. We believe that a significant accomplishment of this symposium is the identification of some of the barriers and problems in neurolaryngology, which we hope will stimulate interest in this rather new field by colleagues and young researchers who will study and overcome them.

We, the moderators, would like to express our sincere appreciation to each contributor to this groundbreaking, original work. On behalf of the contributors to this symposium, we are particularly grateful to the president of this congress, Professor Emeritus and President of Kurume University, Dr Minoru Hirano, and to the board of directors, delegates, and members of our society for giving us the opportunity to organize the symposium.

Hajime Hirose, MD
Yoshikazu Yoshida, MD
Moderators

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NEUROTRANSMITTERS AND NEUROMODULATORS INVOLVED IN LARYNGEAL INNERVATION

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The distribution and role of neurotransmitters and neuromodulators in laryngeal innervation are reviewed, and our recent findings regarding the nitrergic innervation of the larynx are demonstrated for the better understanding of the complexity of the laryngeal innervation system. Noradrenergic innervation of the larynx was studied with fluorescence histochemistry and electron microscopy after application of 5-hydroxydopamine. These studies confirmed the existence of noradrenergic innervation for the submucosal glands and blood vessels, and the origin and course of noradrenergic nerve fibers contained in the laryngeal nerves and their destinations in the larynx. Cholinergic innervation of the larynx has not been clarified in detail. Many kinds of neuropeptides have been demonstrated to be involved in laryngeal innervation. Vasoactive intestinal polypeptide originating from intralaryngeal ganglionic neurons participates in laryngeal vasodilation and reduction of laryngeal seromucous secretion. Neuropeptide Y nerve fibers are few in the larynx, and most originate from the superior cervical ganglion. They are distributed around the large or medium-sized blood vessels, especially arteries. They are also associated with excretory structures. Substance P was the first neuropeptide found to be a sensory neurotransmitter in the laryngeal afferent system. It is also involved in regulation of laryngeal blood flow and secretion. Calcitonin gene–related peptide is associated with the sensory, autonomic, and motor innervation of the larynx. The majority of enkephalin nerve fibers are located close to excretory structures, although no information on the physiological significance of enkephalin is available. In addition to the above neuropeptides, the peptides histidine isoleucine, histidine methionine, and helospectin have been shown to exist in the larynx. The nitrergic innervation of the larynx has been recently studied with NADPH-diaphorase histochemistry and immunohistochemistry using antiserum against nitric oxide synthase. Nitric oxide originates from the neurons in the intralaryngeal ganglia and is believed to modulate blood flow and secretion of the larynx. It controls the laryngeal exocrine secretion in cooperation with intrinsic vasoactive intestinal polypeptide and/or extrinsic calcitonin gene–related peptide. Nitric oxide from the nodose ganglion may modulate nociception of the larynx. The existence of nitrergic neurons located in the intrinsic laryngeal muscles has been demonstrated. Many of them are bipolar or pseudounipolar, so they might be sensory in nature. The effect of injury of the recurrent laryngeal nerve on the induction of nitric oxide synthase in the laryngeal motoneurons is also discussed.

KEY WORDS — laryngeal innervation, neuromodulators, neuropeptide, neurotransmitters, nitric oxide.

INTRODUCTION

The laryngeal innervation system is very complex, and many problems still remain to be solved. Investigation of the neuroactive substances of the larynx would provide important clues for clarifying its innervation system.

Neuroactive substances in the nervous system are generally classified as either neurotransmitters or neuromodulators, depending on the duration and the functional implications of their actions.[1] Substances with typical neurotransmitter roles cause phasic postsynaptic responses that are both quick in onset and relatively short in duration. In contrast, modulatory actions of neuroactive substances are distinguished by their prolonged duration and the ability to modulate neuronal response to other inputs.

In spite of the apparent simplicity, direct cholinergic transmission at the neuromuscular junction (NMJ) is modulated in complex ways by several substances. For example, at the skeletal NMJ, activation of α-adrenergic receptors on the presynaptic nerve terminal was found to increase the amount of transmitter released by an action potential. Varicosities along sympathetic axons in skeletal muscle are not specifically juxtaposed to NMJs. Sympathetic axons course randomly through muscle and release noradrenaline (NA) from varicosities scattered along their lengths. Accordingly, NA must diffuse some distance from its site of release to reach receptors on the axon terminal and the muscle fiber. In addition, NA released from 1 varicosity may affect transmission at many NMJs. Thus, the specificity of NA's actions is achieved not by precise anatomic connections, but by the nature and distribution of the receptors to which it binds.[2]

Transmitters have been divided into 2 groups. One

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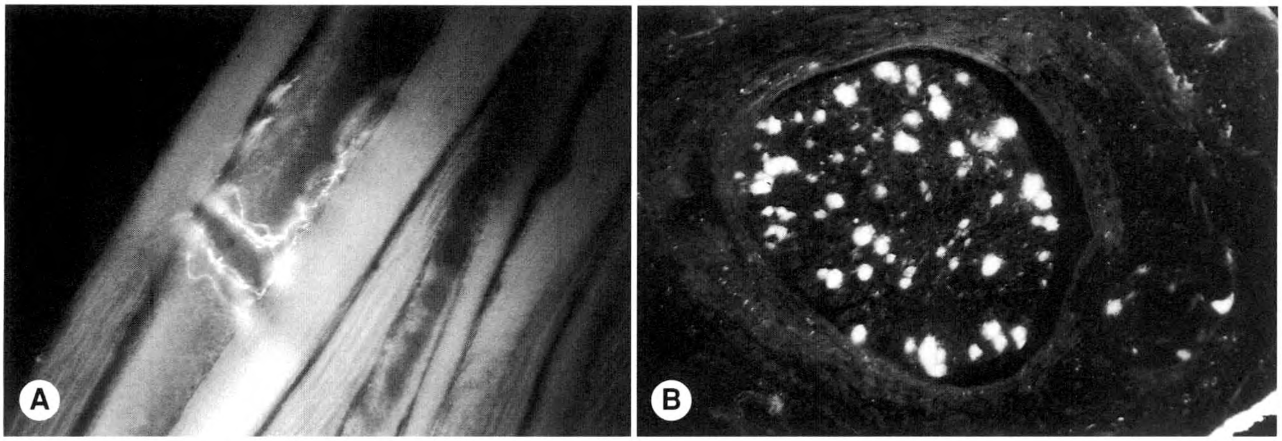

Fig 1. Canine noradrenergic nerve fibers detected by fluorescence histochemistry. A) Distributed around blood vessel in thyroarytenoid muscle (original ×140). B) Contained in recurrent laryngeal nerve (original ×70).

group consists of the low–molecular weight transmitters such as acetylcholine (ACh), epinephrine, NA, dopamine, serotonin, histamine, adenosine triphosphate, and the amino acids γ-aminobutyric acid, glutamate, and glycine. The second group of transmitters are the neuropeptides, more than 50 of which have been identified in the mammalian central nervous system.[2]

Nitric oxide (NO), which is a common air pollutant, a cigarette smoke constituent, and a toxic gas, has recently been recognized to serve a variety of functions in vertebrate cells, ranging from digestion and blood pressure regulation to antimicrobial defense.[3,4] In the nervous system, NO is now well known to carry important information. It first attracted researchers as a messenger molecule that helped neurons store and retrieve information — a function vital to learning and memory.[3] It is now considered to be a transmitter or signaling molecule in a number of distinct subpopulations of neurons in the central and peripheral nervous systems.[5] It is the smallest, lightest molecule and the first gas known to act as a biological messenger in mammals. In the presence of oxygen, NO may vanish a few seconds after it forms, although its life span in the human body is unknown.[3] These characteristics suggest that NO is a very special neuromodulator, acting differently from other neuromodulators.

We have studied the chemical neuroanatomy for the better understanding of the complexity of the laryngeal innervation system. We herein review the involvement of classic neurotransmitters and neuropeptides in the laryngeal innervation system, as well as demonstrating our recent findings regarding the nitrergic innervation of the larynx of rats and dogs.

CLASSIC NEUROTRANSMITTERS

In the laryngeal innervation system, ACh and NA have been demonstrated to participate as classic transmitters in autonomic and motor innervation.

Autonomic Innervation. The first study on the classic neurotransmitters involved in laryngeal innervation was performed with fluorescence histochemistry and electron microscopy with application of 5-hydroxydopamine (5-OHDA) to determine the noradrenergic innervation of canine laryngeal glands.[6] Noradrenergic nerve fibers with varicosities were found to localize around the base of acini in the laryngeal glands. Varicosities containing dense-cored vesicles observed under electron microscopy after application of 5-OHDA are highly specific for noradrenergic terminals.[7] Electron microscopy revealed varicosities containing both small and large dense-cored vesicles close to blood vessels, acinar cells, and myoepithelial cells in the submucosal gland region in dogs treated with 5-OHDA. This study clearly demonstrated the existence of noradrenergic innervation for the canine submucosal laryngeal glands.

Another study on the noradrenergic innervation of the canine larynx was subsequently performed with fluorescence histochemistry.[8] This study clarified the origin and course of noradrenergic nerve fibers contained in laryngeal nerves and their destinations in the larynx (Fig 1). A large number of noradrenergic nerve fibers were demonstrated to be contained in the laryngeal nerves: the internal and external branches of the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN). These nerves were also demonstrated to be the only noradrenergic supply to the larynx. The SLN received noradrenergic nerve fibers from the superior cervical ganglion (SCG) below the nodose ganglion (NG). The RLN received noradrenergic nerve fibers originating from the middle cervical ganglion directly and those originating from the SCG via the vagus nerve. This study clearly ruled out the popular view that sympathetic nerve fibers reach the larynx via the blood vessels. The sympathetic innervation of the canine larynx was investigated with tyrosine hydroxylase (TH) immunohistochemistry.[9] This technique has several advantages over fluorescence histochemistry: tissue sections can be kept permanently, the sensitivity is higher, counterstaining is possible, and specimens are also available for electron microscopic investigations. This study using TH immunohistochemistry confirmed the results obtained in the previous studies performed by fluorescence histochemistry. In addition, it demonstrated that only arteries and arterioles are innervated by noradrenergic nerve fibers in the laryngeal vessels. Those results show that vascular glomeruli in the submucosa, which were considered to have sympathetic innervation,[10] are not innervated by noradrenergic nerve fibers. Using TH immunohistochemistry in combination with the retrograde tracer technique, Uno et al[11] demonstrated that neurons containing TH in the NG participate in the regulation of chemoreception in the larynx. Although ACh is well known as a classic transmitter for parasympathetic innervation, there have been no systematic studies on the cholinergic innervation of the larynx. A morphological technique to determine cholinergic innervation could use acetylcholinesterase (AChE) histochemistry and choline acetyltransferase immunohistochemistry. Choline acetyltransferase immunohistochemistry has demonstrated various types of cholinergic innnervation in the central nervous system. This technique, however, does not work well in the peripheral nervous system, although the reason for this difference between the central and peripheral nervous systems is not yet clear. The improvement of this technique is essential for the investigation of cholinergic innervation of the larynx.

The existence of intralaryngeal ganglia, putative parasympathetic ganglia in the larynx, was already known in the 1930s.[12] Yoshida et al[13] reported that 6 to 8 large ganglia containing 50 to 80 ganglionic neurons per ganglion in the paraglottic space and 4 to 6 small ganglia involving 5 to 25 cells in each ganglion dorsal to the posterior cricoarytenoid muscle are present in the cat. One to 3 small ganglia including 15 to 25 neurons around the inferior laryngeal nerve were also observed. These neurons, totaling 600 to 800, were oval and had an average size of 25 μm. Many were AChE-positive, confirming that most of these ganglionic neurons are cholinergic. The distribution of the cholinergic nerve fibers in the larynx originating from these ganglia should be clarified in the future.

Motor Innervation. The AChE activity has been investigated in the NMJs of normal and denervated intrinsic laryngeal muscles, showing the participation of ACh in the motor innervation of the intrinsic laryngeal muscles.[14-16] These reports demonstrate that the distribution of the NMJ on the muscle fibers of the intrinsic laryngeal muscles is different from the distribution on other mammalian skeletal muscles, which have the NMJ at the midpoint of the muscle fibers. This difference may be related to regulation of the complex functions of the larynx, although ultrastructural features of the NMJ in the intrinsic laryngeal muscles are basically the same as those of other skeletal muscles.[16]

Electron microscopy with application of 5-OHDA has revealed that nerve terminals at previously denervated NMJs of the feline intrinsic laryngeal muscles are reinnervated by noradrenergic nerve fibers originating from the ipsilateral SCG.[17] It would be worth examining whether this phenomenon is characteristic only of intrinsic laryngeal muscle or whether it can be generally applied to all other skeletal muscles.

NEUROPEPTIDES

One of the most important recent developments in neurobiology is the recognition of neuroactive peptides, which have widespread distribution in both the central and peripheral nervous systems. Like classic neurotransmitters, peptides can be identified as neuroactive substances only by meeting certain criteria. The neuropeptides may have neurotransmitter-like properties, but more commonly, they act as neuromodulators by potentiating or blocking the effects of other neurotransmitters. The immunohistochemical method of using monoclonal antibodies with high sensitivity and specificity introduced by Sternberger et al[18] has been a great advantage for the detection and localization of neuropeptides in the neural tissue.

Vasoactive intestinal polypeptide (VIP) was found in 1978 to be a neuropeptide distributed in the larynx.[19] A variety of neuropeptides have since been shown to participate in the laryngeal innervation system of many species. Radioimmunoassay of the human larynx revealed that the most prominent peptide is VIP, especially in the ventricular folds, followed by substance P (SP) and neuropeptide Y (NPY). The calcitonin gene–related peptide (CGRP) level is close to the detection limit.[20]

Vasoactive Intestinal Polypeptide. Uddman and Sundler[19] reported scattered VIP nerve fibers around seromucous glands and small blood vessels in the larynges of guinea pigs, rabbits, and cats. These findings were subsequently confirmed in humans[21] and dogs.[22] Vasoactive intestinal polypeptide causes vasodilation and reduction of seromucous secretion. The origin of these VIP nerve fibers is considered to

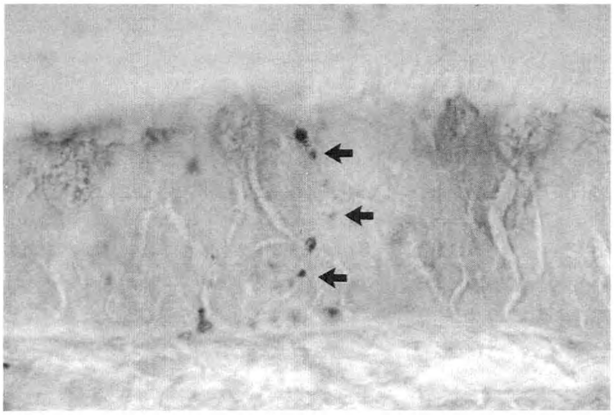

Fig 2. Substance P nerve fiber with varicosities (arrows), detected in canine laryngeal epithelium by immunohistochemistry with antiserum against substance P (original ×200).

be ganglionic cells in the intralaryngeal ganglia, and this fact would indicate that these nerve fibers are participating in postganglionic parasympathetic innervation.[23] Many ganglionic cells in the intralaryngeal ganglia of rats,[23-26] dogs,[26] and cats[13,27,28] have been demonstrated to contain VIP: 97% in dogs[26] and 91% in cats.[27]

The precise localization of VIP nerve fibers in the cat laryngeal glands was demonstrated by immunoelectron microscopy.[29] Some VIP nerve fibers were found to contact the basal lamina, while others were found to pierce the basal lamina and run intercellularly among the adjoining glandular cells without making synaptic contacts with them.

Neuropeptide Y. Neuropeptide Y is known to coexist with NA in perivascular nerves and acts as a powerful vasoconstrictor.[30] Although NPY nerve fibers are few in the larynx,[31,32] they have been reported to be distributed around blood vessels of the larynx in rats,[23,31] dogs,[22,26] and humans.[20,21,33] The NPY nerve fibers are distributed between the media and the adventitia[33] of large and medium-sized blood vessels, especially arteries.[21,23,33]

A few NPY nerve fibers were also detected in association with excretory structures in humans[20,21,32] and cats.[29] There is disagreement over the distribution of NPY nerve fibers in the laryngeal glands of rats. Luts et al[31] reported that no NPY nerve fibers were distributed in the glandular region of rats, whereas Domeij et al[23] found NPY nerve fibers in rat laryngeal glands. Tanaka et al[29] estimated that the ratio of VIP to NPY nerve fibers distributed in the cat laryngeal glands is 20:1. The precise localization of NPY nerve fibers in the glandular region is also different from that of VIP nerve fibers. The NPY nerve fibers never terminate or penetrate the basal lamina of the glands.[29] The involvement of NPY in the regulation of laryngeal exocrine secretion seems not to be noteworthy.

The origin of NPY nerve fibers in the larynx has been studied. Some NPY-immunoreactive cells have been detected in the intralaryngeal parasympathetic ganglion of rats,[23,25,31] dogs,[26] cats,[13,27,28] and humans,[32] but their number is small compared with the number of VIP-immunoreactive cells. Many postganglionic neurons are NPY-immunoreactive in the SCG,[34] the main source of sympathetic nerve fibers for the larynx.[8] Luts et al[31] found that the majority of NPY nerve fibers in the vocal cords of rats emanate from the SCG and the stellate ganglion, and a minor population of NPY nerve fibers originate from local ganglia. Domeij et al[23] also reported that excision of the SCG did not affect the distribution of NPY nerve fibers in association with the acini and ducts in the perichondrium or in the lamina propria at any level of the larynx.

Substance P. Substance P was the first neuropeptide, in 1985, to be discovered as a candidate sensory neurotransmitter in the laryngeal afferent system, by Hisa et al.[35] The distribution of SP nerve fibers in the laryngeal epithelium has been clarified in rats,[36] cats,[37] dogs,[22,26,35,38,39] monkeys,[40] and humans.[20] Substance P nerve fibers with varicosities extended into the epithelial layer (Fig 2). These nerve fibers were demonstrated to ascend from the basement membrane to the free surface, up to 1.6 µm from the free surface of the epithelium between the epithelial cells. They also form tiny knoblike swellings at the tip of the nerve fibers, as seen by electron microscopic immunohistochemistry.[38] The terminal SP nerve fibers within the epithelium disappeared after bilateral denervation of the canine superior and inferior laryngeal nerves, indicating that these SP nerve fibers originate from neurons in the NG and/or jugular ganglion.[26] Hisa et al[41] applied immunohistochemistry and a retrograde tracing method using cholera toxin subunit B–conjugated gold (CTBG) to discover that 24.5% of afferent neurons from the internal branch of the SLN (SLNI) in the canine NG are SP-immunoreactive.

Substance P is also involved in regulation of laryngeal blood flow and secretion. Substance P nerve fibers have been detected around the laryngeal glands and blood vessels in rats,[36] cats,[37] dogs,[22,26,35,38] and humans.[20] Substance P is a powerful endothelium-dependent vasodilator.[42] Regarding the involvement of SP in airway secretion, it is thought that SP may stimulate constriction of submucosal gland secretory tubules and ducts, resulting in the expulsion of mucus stored therein, rather than stimulating increased mucus production per se.[43]

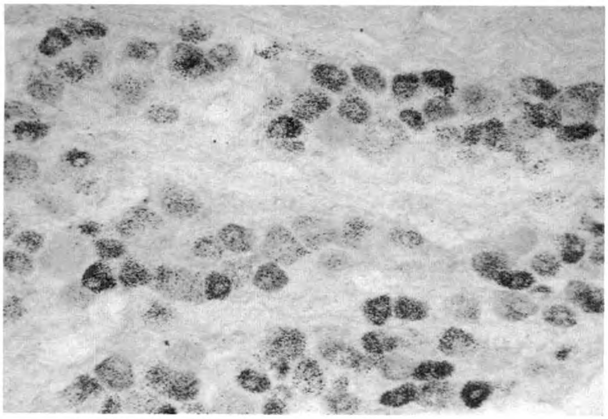

Fig 3. Canine nodose ganglion stained immunohistochemically with antiserum against calcitonin gene–related peptide (CGRP) after application of cholera toxin subunit B–conjugated gold (CTBG) to internal branch of superior laryngeal nerve (original ×40). Neurons with CGRP immunoreactivity were identified by presence of brown diamidinobenzidine product in their cytoplasm, and neurons labeled with CTBG were identified by presence of black dots in their cytoplasm. Many CTBG-labeled neurons have CGRP-like immunoreactivity.

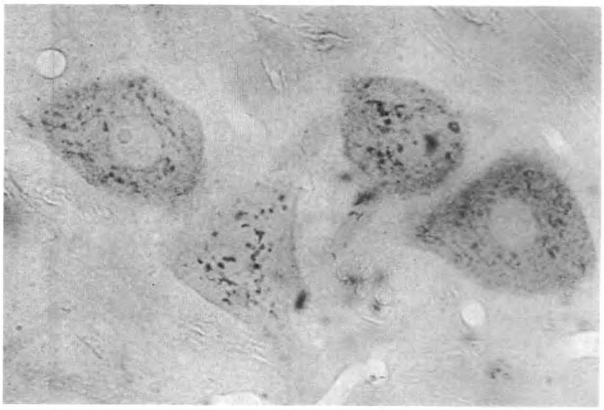

Fig 4. Motor neurons with CGRP-like immunoreactivity in canine nucleus ambiguus, detected by immunohistochemistry with antiserum against CGRP (original ×200).

Domeij et al[36] reported that SP nerve fibers in the larynx almost disappeared after unilateral vagotomy in the rat. In contrast to this report, SP nerve fibers around the blood vessels of dogs remained in the larynx after bilateral denervation,[26] and this finding suggests that these SP nerve fibers are of intrinsic origin. The different results in these similar studies may be due to species differences. The existence of SP-immunoreactive cells in the parasympathetic intralaryngeal ganglion has been reported in dogs,[26] cats,[13,27,28] and humans,[44] although the number of cells is very small. However, there have been no reports indicating the existence of SP-immunoreactive cells in the intralaryngeal parasympathetic ganglion of rats.

Calcitonin Gene–Related Peptide. Calcitonin gene–related peptide participates in the sensory, autonomic, and motor innervation of the larynx.[45] The combination technique of immunohistochemistry and retrograde tracing using CTBG as a tracer revealed that CGRP is, according to current evidence, the main neurotransmitter of the afferent system in laryngeal innervation (Fig 3).[41] Distribution of CGRP nerve fibers in the laryngeal epithelium has been demonstrated in rats,[31,36,46] cats,[37] dogs,[22,45] monkeys,[40] and humans.[20] Some of these fibers with varicosities exist between epithelial cells and appear to have free endings. The distribution of these nerve fibers is different in the region of the larynx, and this difference is constant among many species.[22,36,37,40,45] Calcitonin gene–related peptide nerve fibers were found in abundance in the epiglottis and subglottis. In the glottis, abundant CGRP nerve fibers were observed in the epithelium of the posterior glottis, although there were very few in the anterior glottis. This difference in the distribution pattern is reasonable: primary afferent information from the epiglottis and subglottis is important for the laryngeal reflex. If there were sensory reception in the anterior glottis, it might cause incorrect motion of the vocal cords at phonation.

Calcitonin gene–related peptide nerve fibers were also found to be distributed in blood vessels as well as glandular regions in rats,[36,46] dogs,[22,26,45] cats,[37] and humans.[20] In contrast to SP-induced vasodilation, CGRP generally causes endothelium-independent vasodilation by a direct effect on vascular smooth muscle.[42] The CGRP-induced vasodilation follows a prolonged time course; therefore, this neuropeptide might be expected to play the dominant physiological role in regulation of airway blood flow.[47] On the other hand, CGRP is reported to elicit only a small and transient increase in transepithelial short-circuit current and plays little physiological role in maintaining airway hydration.[42]

Most CGRP nerve fibers in the larynx are considered to be not of intrinsic origin, but of extrinsic origin: the NG.[27,46,48] No CGRP-immunoreactive cells were detected in the intralaryngeal parasympathetic ganglia of rats,[36] cats,[27] or dogs.[26] Hisa et al[41] reported that 81.5% of afferent neurons from the SLNI located in the NG are CGRP-immunoreactive — more than 3 times the number of SP-immunoreactive cells. This result explains the finding that the number of CGRP nerve fibers in the epithelium is greater than the number of SP nerve fibers.[45,49]

Calcitonin gene–related peptide is the only neuropeptide detected in the somatic motor neurons. The motor neurons in the nucleus ambiguus (nAmb) for the pharyngeal and laryngeal striated muscles in rats[50] and dogs[51] are known to contain CGRP (Fig 4). Calcitonin gene–related peptide enhances muscle contraction and leads to a concomitant increase in the cyclic adenosine monophosphate level during stimulation of the nerve fibers or direct stimulation of the muscle.[52-54] It also stimulates the synthesis of ACh receptors.[55] In addition to these functions, CGRP has a neurotrophic function. Treatment with CGRP suppresses terminal sprouting in a dose-dependent way, so that CGRP is possibly an antisprouting agent.[56] Neuromuscular junctions with CGRP immunoreactivity in the intrinsic laryngeal muscles have been demonstrated in rats,[48] cats,[16] and dogs.[45] The localization of CGRP in NMJs was ultrastructurally studied by electron microscopic immunohistochemistry.[16] The CGRP immunoreactivity was restricted to the nerve terminals, while no reaction was seen in the primary and secondary synaptic clefts or the sarcolemma; hence, CGRP may affect the neuromuscular transmission or may be a neurotransmitter itself.

Enkephalin. Distribution of enkephalin (ENK) in the larynx has been demonstrated in rats[24,25] and dogs.[22,26] Few ENK nerve fibers were found around the blood vessels, and none were observed in the laryngeal epithelium. The majority of ENK nerve fibers were located close to the ducts and acini of the glands. The physiological significance of ENK in the airway is largely unknown, and no information is available for the larynx.[25]

Enkephalin-immunoreactive cells were found in the intralaryngeal ganglia of rats,[25] cats,[27] and dogs.[26] That the number and distribution of ENK nerve fibers in the laryngeal tissue in sympathectomized and vagotomized animals were similar to those found in control animals indicates that ENK nerve fibers in the larynx are intrinsic in origin.

Others. In addition to the above neuropeptides, peptide histidine isoleucine,[24] peptide histidine methionine (PHM),[20] and helospectin[32,57] have been demonstrated in the human larynx. The structural homology of VIP, PHM, and helospectin suggests comparable biological activities. These peptides stimulate amylase release in pancreatic acini of the guinea pig with the following potencies: VIP greater than helospectin greater than PHM.[57] Helospectin relaxes phenylepinephrine-contracted vessels to the same extent as VIP, but with a lower potency.[58] These reports suggest that these peptides may participate in regulation of secretion and/or blood flow in the larynx.

Coexistence of Neuropeptides. Coexistence of neuropeptides in the laryngeal innervation system has been investigated. Both VIP and NPY were reported to coexist in some nerve fibers located in the walls of arteries and arterioles in the lamina propria of the rat larynx and in the nerve fibers close to the acini and ducts of the glands.[23] In rats, nerve fibers with both VIP and NPY in the glands and the lamina propria were often detected near ENK-containing nerve fibers, although VIP and NPY nerve fibers were more abundant than those with ENK.[25] A high degree of coexistence of SP and CGRP was found in the nerve fibers of the rat larynx, and unilateral sympathectomy did not affect the pattern of SP and CGRP innervation in the larynx, whereas after vagotomy, ipsilateral SP and CGRP innervation almost disappeared in the upper parts of the epiglottis and aryepiglottic folds.[36]

Coexistence of VIP and NPY in the ganglionic cells of the intralaryngeal ganglion was demonstrated in rats,[23,25] cats,[27] and dogs.[26] Thirty-six percent of cells containing VIP were also NPY-positive in dogs, 7% were ENK-positive, and 13% were SP-positive.[26] Fourteen percent of VIP-positive cells contained both NPY and SP. Coexistence of VIP and NPY in ENK-positive cells was also reported in rats.[25] In cats, 27% of VIP-positive cells were shown to contain ENK, and 5% were also positive for both ENK and SP.[27]

OUR RECENT FINDINGS REGARDING NITRERGIC INNERVATION OF LARYNX

Using nicotinamide adenine dinucleotide phosphate–diaphorase (NADPHd) histochemistry and immunohistochemistry using antiserum against nitric oxide synthase (NOS), we have investigated the participation of NO in the laryngeal innervation of rats and dogs[59-61] and are currently investigating the effect of injury on the induction of NOS in the laryngeal innervation.

Histochemical Procedures. It is impossible to demonstrate NO directly in the tissue, since NO may vanish a few seconds after it forms and is not stored in neurons. It is synthesized from the amino acid L-arginine by NOS, and the presence of NOS in the tissue should indicate the existence of NO. The presence of NOS in nerve tissue can be shown through an immunohistochemical procedure using commercially available antiserum against NOS. An NADPHd histochemical technique is also used to show the presence of NO. It is based on the presence in certain neurons of an enzyme that can catalyze the NADPH-dependent conversion of a soluble tetrazolium salt to an insoluble, visible formazan.[62] Hope et al[63] found that NOS and NADPHd activities copurify to homogeneity and that both kinds of activity can be immunoprecipitated with an antibody recognizing neuronal NADPHd. Furthermore, NOS was

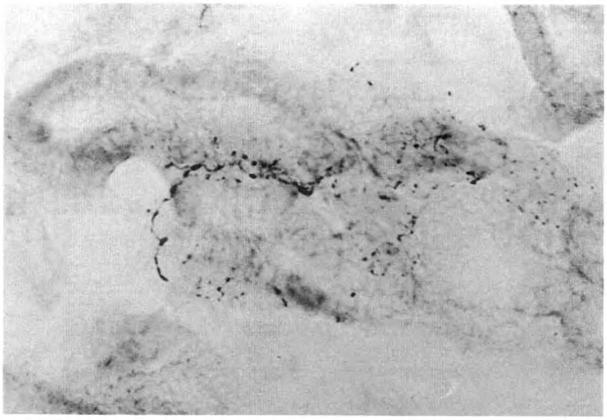

Fig 5. Nicotinamide adenine dinucleotide phosphate–diaphorase (NADPHd)–positive nerve fibers distributed around canine laryngeal glands, detected by NADPHd histochemistry (original ×80).

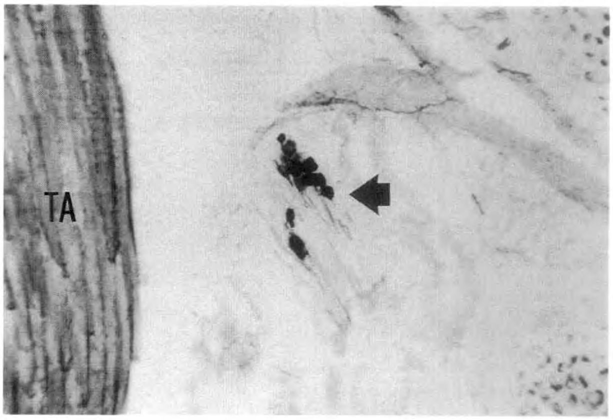

Fig 6. Intralaryngeal ganglion of dog (arrow), detected by NADPHd histochemistry (original ×25). Many neurons in ganglion are positive for NADPHd histochemistry. TA — thyroarytenoid muscle.

competitively inhibited by the NADPHd substrate, nitroblue tetrazolium. Thus, neuronal NADPHd is considered to be an NOS. Therefore, NADPHd histochemistry could provide a specific histochemical marker for neurons producing NO.

Distribution of Nitrergic Nerve Fibers in Larynx. We have reported that the findings in the larynx obtained by NADPHd histochemistry corresponded well with those obtained by NOS immunohistochemistry, indicating that NADPHd is also an NOS in the laryngeal innervation system of rats[59] and dogs.[60,64] The NADPHd histochemistry is simpler and less expensive than NOS immunohistochemistry. We have also shown that this technique is useful for demonstrating colocalization of the neuropeptides and NOS after sequential immunohistochemical procedures using antisera against neuropeptides.

Nerve fibers positive for NADPHd are distributed in every region of the larynx, and NADPHd-positive nerve fibers with varicosities are found in the epithelia of the laryngeal mucosa. Most of these fibers with varicosities reached the surface of the epithelium and appeared to be free-ended. It has been suggested that NO activates primary afferents that modulate nociceptive behavior in the peripheral nervous system.[65-67] The distribution of SP and CGRP nerve fibers with varicosities, possibly afferent nerve fibers, in the epithelium of the laryngeal mucosa has been described previously.[35,45] The morphological pattern of the NADPHd-positive nerve fibers in the epithelium corresponded well with SP and CGRP nerve fibers. Additionally, many neurons in the NG, the main source of the afferent nerve fibers for the larynx, are well known to contain NOS.[68] Under these circumstances, the NADPHd-positive nerve fibers in the epithelium of the laryngeal mucosa are considered to be afferent nerve fibers, and suggest that NO modulates the nociception of the larynx.

A plexus of NADPHd nerve fibers was reported to be found frequently in the lamina propria, and some of these fibers were clearly associated with blood vessels of the rat larynx.[59] This association had no relation to the size of the blood vessels. Also, NADPHd nerve fibers were found in the region of laryngeal glands, and some of these fibers appeared to clearly terminate in glandular cells. These findings were also found in dogs and suggest that NO controls laryngeal blood flow and secretion (Fig 5).

Distribution of Nitrergic Neurons in Larynx. The localization and chemical features of intralaryngeal ganglia, possibly parasympathetic, have been studied mainly with morphological techniques. A cluster of NADPHd-positive neurons was found, mainly in the paraglottic space. We have already reported that many neurons of intralaryngeal ganglia in rats[59] and dogs[61] are nitrergic, using NOS immunohistochemistry and NADPHd histochemistry (Fig 6). Nitric oxide has been considered to be an endogenous modulator of cholinergic neurotransmission in the guinea pig airway.[69] All neurons in the intralaryngeal ganglia of rats have been reported to be AChE-positive.[25] These studies suggest that nitrergic neurons in the intralaryngeal ganglia are parasympathetic in nature and that NO is also an endogenous modulator of cholinergic neurotransmission in the larynx. This idea is also supported by the findings that blood vessels and submucosal glands in the larynx are supplied with nitrergic nerve fibers. Nitric oxide originating from the neurons in the intralaryngeal ganglia is an endogenous modulator of cholinergic neurotransmission in the regulation of blood flow and secretion in the larynx.

A striking recent finding is the existence of nitrergic neurons located in the intrinsic laryngeal muscles.

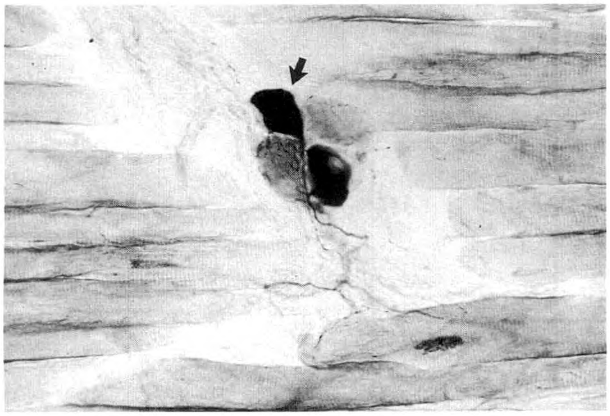

Fig 7. Ganglionic neurons in canine posterior cricoarytenoid muscle, detected by NADPHd histochemistry (original ×80). Arrow shows positive pseudounipolar–shaped neuron. Although neuromuscular junctions are positive for NADPHd histochemistry, they are not associated with fine varicose NADPHd-positive nerve fibers.

We have reported that cells intensely stained by NADPHd histochemistry were found between the striated muscle fibers of the canine intrinsic laryngeal muscles (Fig 7).[60] Many of these cells were bipolar or pseudounipolar in form. The findings obtained by NOS immunohistochemistry corresponded well with those obtained by NADPHd histochemistry, and this correspondence indicates that NADPHd in the ganglion in the intrinsic laryngeal muscles is an NOS. Although the existence of the intralaryngeal ganglion is well known, there have been no reports referring to the neurons located in the intrinsic laryngeal muscles.

Neuhuber et al[70] and Worl et al[71] demonstrated that a majority of motor end plates in the rat esophagus are associated with fine varicose NADPHd-positive nerve fibers originating from esophageal myenteric neurons and that NOS immunoreactivity is identical to NADPHd activity in these neuronal cell bodies and fine varicose fibers. However, the motor end plates in the intrinsic laryngeal muscles are not the target of these ganglionic cells, since they were not associated with the fine varicose NADPHd nerve fibers. The ganglionic cells located in the striated muscle layer have been energetically studied in the tongue of several mammalian and nonmammalian species.[72-76] The cholinergic nature of the lingual ganglionic cells in chicks was demonstrated by showing that they exhibit a strong reaction to AChE.[73] Inoue and Kitada[76] observed degeneration in the presynaptic boutons impinging upon the neuronal perikarya in the lingual branch of the glossopharyngeal nerve after eliminating preganglionic parasympathetic input to the frog tongue by cutting the glossopharyngeal nerve proximal to the jugular ganglion. However, the morphological characteristics — that many nitrergic neurons are bipolar or pseudounipolar in form — suggest the possibility that these cells might be sensory in nature. Further studies should be done to clarify the functional characteristics of these cells.

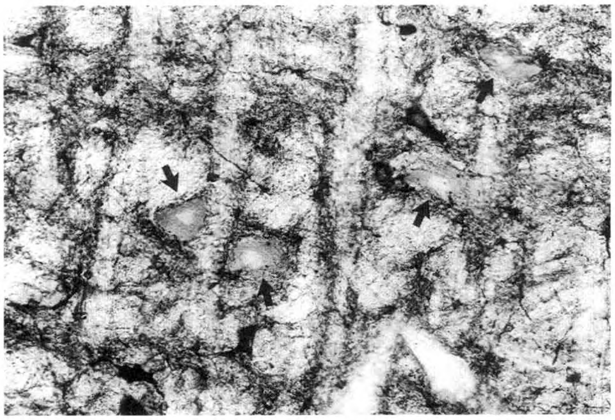

Fig 8. Motoneurons in nucleus ambiguus provided for NADPHd histochemistry (original ×80). Motoneurons (arrows) are not NADPHd-positive.

Coexistence of NOS and Neuropeptides in Laryngeal Innervation. Many studies have demonstrated a relationship between NO and neuropeptides, especially VIP, in the innervation of various organs in different species.[77-84] We investigated the participation of VIP and CGRP in nitrergic innervation for canine laryngeal glandular secretion using a double staining technique of NADPHd and VIP or CGRP immunohistochemistry,[61] since a dense distribution of VIP and CGRP nerve fibers has been demonstrated in the laryngeal glandular region in dogs[22,45] and cats.[29]

Double staining in this study revealed that NADPHd reactivity and VIP- or CGRP-like immunoreactivity are colocalized to some nerve fibers distributed around the glandular region. A VIP-like immunoreactivity also colocalized to many neurons of the intralaryngeal ganglia, and no NADPHd-positive neurons had CGRP-like immunoreactivity.[61] This finding suggests that NO participates in the neural control of laryngeal exocrine secretion in cooperation with intrinsic VIP and/or extrinsic CGRP. Colocalization of VIP in nitrergic neurons has been demonstrated in various organs. Both NO and VIP appear to contribute to the nonadrenergic noncholinergic (NANC) innervation.[78,79,81-83] However, VIP-positive nitrergic nerve fibers in the laryngeal submucosal glands are considered not to be NANC nerve fibers, but rather, cholinergic, since the neurons in the intralaryngeal ganglia of rats have been reported to contain AChE.[25] This observation is in contrast to those in rat enteric neurons, wherein NOS does not colocalize with AChE.[78] Nitric oxide is also reported to be an endogenous modulator of cholinergic neurotransmission in the guinea pig airway[69] and a neuronal comediator of VIP and/or cholinergic vasodilation.[77]

Nitrergic nerve fibers in the respiratory tract of the guinea pig have been reported to lack CGRP.[81] The neurons in the intralaryngeal ganglia do not appear to be the source of nitrergic nerve fibers containing CGRP, since they lack CGRP.[61] The present findings are in agreement with the observation that CGRP was absent in neurons of the intralaryngeal ganglia in cats.[13,26] In rats, many neurons in the NG, a vagal sensory ganglion, contain NOS,[85] and a considerable number of neurons in the NG of the canine SLNI, the main pathway of sensory nerve fibers for the larynx, contain CGRP.[41] These findings suggest that the CGRP-positive nitrergic nerve fibers in the canine laryngeal glands are derived from sensory neurons in the NG. Both sympathetic and vagal sensory ganglia have been demonstrated to be a source of inhibitory NANC nerve fibers in the lower airway,[86] in contrast to parasympathetic postganglionic neurons in the gall bladder[87] and pelvic organs.[88] The CGRP-positive nitrergic nerve fibers detected in the canine laryngeal glands are also considered to be NANC nerve fibers of the laryngeal glands.

Effect of Injury of RLN on Induction of NOS in Laryngeal Motoneurons. Reports have demonstrated that NOS, undetectable in motoneurons under normal conditions, is induced in motoneurons after traumatic injury.[88-91] Although axotomy induces NOS in motoneurons in some cranial nuclei, it does not induce NOS in spinal motoneurons, and this finding suggests differences in the NOS expression between motoneurons of the cranial and spinal nerves after traumatic injury.[91] Only 1 experimental study has been reported on the NADPHd expression of motoneurons in the nAmb after vagotomy. We are now engaged in examining the effect of injury of the canine RLN on the induction of NOS in the laryngeal motoneurons. We started with examining whether NADPHd activity is induced in the laryngeal motoneurons after the avulsion of the ipsilateral RLN of dogs by NADPHd histochemistry in combination with the retrograde tracer technique.

Avulsion was performed at the level of the first tracheal ring of the RLN, and the tracer was injected into the proximal part of the avulsion. Ten days after surgery, the dogs were painlessly sacrificed and the ipsilateral nAmb was examined. Although the neurons in the nAmb could be detected with NADPHd histochemistry, these neurons were very lightly stained and clearly distinguished from other NADPHd-positive neurons (Fig 8). All the labeled motoneurons labeled 10 days after avulsion of the ipsilateral RLN were very lightly stained for NADPHd, as were the unlabeled motoneurons in the contralateral nAmb in the same section.

This result suggests that NOS is not induced in the laryngeal motoneurons after avulsion of the RLN. Gonzalez et al[88] demonstrated that cervical vagotomy increased NADPHd histochemical staining in the neuronal perikarya of the ipsilateral dorsal motor nucleus of the vagus and the rostral part of the nAmb. In contrast, spinal motoneurons express NOS after ventral root avulsion, but not after ventral root transection.[89]

Induction of NOS to the motoneurons after injury is now implicated in neuronal degeneration and plasticity related to NO. The spinal motoneurons in adult rats also die when NOS is induced after ventral root avulsion.[90] However, nitroarginine, a specific inhibitor of NOS, reduces motoneuron death of spinal motoneurons, and this finding suggests that NO produced by NOS is responsible for the death of injured motoneurons as a killer protein.[90] Wu et al[92] reported that implantation of a peripheral nervous system graft significantly enhances the survival of motoneurons following avulsion by inhibiting the expression of NOS due to avulsion in all motoneurons that regrow into the graft.

The pathophysiology of RLN paralysis remains to be clarified. Although some surgeons anastomose the cut end and/or implant other peripheral nerve tissue when they are obliged to cut or remove the RLN in expectation of normal mobility of vocal cords, recovery of mobility of vocal cords is not successful in most cases. However, vocal cord atrophy is prevented by these procedures. It remains to be determined if this is due to prevention of motoneuron death as Wu et al[92] reported. The expression of NADPHd activity in laryngeal motoneurons after axotomy of RLN and after implantation of peripheral nerve tissue following axotomy is currently under investigation.

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BRAIN STEM NEURAL MECHANISMS FOR VOCALIZATION IN DECEREBRATE CATS

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In order to characterize the brain stem circuitry that produces vocalization, the activities of brain stem respiratory neurons were recorded extracellularly during vocalization induced by electrical stimulation of the periaqueductal gray in decerebrate cats. After the onset of stimulation, the respiratory rhythm ceases, and a preparatory inspiration is induced. Following this initial inspiration, vocalization characterized by increased activities of the intrinsic laryngeal adductor and the major expiratory muscles is induced. During vocalization, most of the dorsal respiratory group inspiratory neurons increase their firing rates in phase with an increase of diaphragm activity. Inspiratory neurons with a continuous discharge pattern in the rostral ventral respiratory group increase their firing rates to augment intrinsic laryngeal abductor motoneurons and bulbospinal inspiratory neurons in the dorsal respiratory group. On the other hand, most of the bulbospinal augmenting expiratory neurons in the Bötzinger complex cease firing just after the onset of periaqueductal gray stimulation for the remainder of the stimulation period. These results indicate that at least some part of the coordinated activations of intrinsic laryngeal and respiratory muscles during vocalization are mediated via the central respiratory neurons that produce breathing.

KEY WORDS — decerebrate cat, extracellular recording, periaqueductal gray, respiratory neurons, vocalization.

INTRODUCTION

Vocalization normally occurs during the expiratory phase and is dependent on expiratory airflow. Therefore, for generating vocalization, characteristic activations of major respiratory, intrinsic laryngeal, and other upper airway muscles, including those of the pharynx, tongue, and lips, are necessary. Their pattern of activation is totally different during vocalization as compared to quiet respiration.[1] In decerebrate cats, repetitive electrical stimulation of the midbrain periaqueductal gray (PAG) induces natural-sounding vocalization.[2-4] After the onset of PAG stimulation, the normal respiratory rhythm ceases, and inspiration is induced. Following the initial inspiratory period, vocalization with increased activities of the adductor of the vocal cords and the major expiratory muscles is induced.

Respiratory neurons, defined as neurons that fire in phase with the respiratory rhythm, are concentrated in 2 locations within the medulla of the brain stem: ventrolateral and dorsomedial medullary areas.[5] The ventrolateral area consists of 3 subgroups extending rostrocaudally, that is, the retrofacial nucleus (Bötzinger complex; BÖT),[6] the ambiguus nucleus (rostral ventral respiratory group; rostral VRG),[7,8] and the retroambigual nucleus (caudal VRG).[9,10] The dorsomedial area is called the dorsal respiratory group (DRG) and corresponds to the ventrolateral nucleus of the solitary tract.[5]

Most of these respiratory neurons are known to control the activities of intrinsic laryngeal and major respiratory muscles directly and/or indirectly during respiration. Bulbospinal expiratory neurons located in the caudal VRG make monosynaptic or oligosynaptic excitatory connections with abdominal and internal intercostal expiratory motoneurons.[9,10] Similarly, bulbospinal inspiratory neurons in the DRG and in the rostral VRG make monosynaptic and oligosynaptic connections with inspiratory motoneurons innervating the diaphragm and external intercostal inspiratory muscles.[5,7,8] Moreover, inspiratory neurons having decrementing (I-Dec) or constant (I-Con) discharge patterns and expiratory decrementing (E-Dec) neurons are located in the rostral VRG and function as propriobulbar neurons that make excitatory (I-Con) and inhibitory (I-Dec, E-Dec) connections with a variety of medullary respiratory neurons.[11-13] Bulbospinal expiratory neurons in the BÖT make monosynaptic inhibitory connections with a variety of medullary respiratory neurons[14,15] and phrenic motoneurons.[16]

A key question regarding the activations of major respiratory and intrinsic laryngeal muscles is whether they are controlled during vocalization via the same

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neurons that are important for their regulation during respiration. In the present study, we recorded the activities of the above-mentioned brain stem respiratory neurons during vocalization, which was induced by electrical stimulation of the PAG in decerebrate cats, to understand the functional role of these neurons in controlling the respiratory and intrinsic laryngeal muscles involved in nonrespiratory and voluntary movements such as vocalization.

HISTORICAL PERSPECTIVE OF CENTRAL MECHANISMS FOR VOCALIZATION

Speech involves 3 mechanical processes: 1) for the power source of the voice signal, expiratory airflow is sent from the alveoli; 2) for the voice source, the larynx modifies the airflow and produces sound; and 3) for the final voice signal, the upper airway structures complete the voice signals. Among these processes, the third process is categorized as articulation (in which the basic sounds are modified into the words of language), and the other 2 processes are categorized as vocalization (which generates the basic sound). Since the process of vocalization is common to both humans and animals, it can be an object of analysis in experiments using animal models.

Since the pioneering study of Magoun et al,[4] which discovered that electrical stimulation delivered near the PAG evoked natural-sounding vocalization, a number of investigators have tried to identify brain structures related to the control of vocalization in different species.[17-21] From these results, it was clarified that electrical stimulation of various parts of the cerebral cortex, with the exception of the limbic cortex, cannot evoke vocalization.[22] Although electrical stimulation can evoke vocalization in different parts of the limbic system, it is achieved most easily in the caudal PAG.[4,23] Moreover, activation of the PAG using excitatory amino acids demonstrated that the PAG is an important neural substrate for the integration of the somatic and autonomic reactions to threatening or stressful stimuli.[24] This result suggested that excitation of the neurons within the PAG induced emotional behaviors, including vocalization. Because the PAG receives inputs from higher brain structures such as the cerebral cortex, thalamus, and limbic structures,[25-28] it was suggested that the PAG serves as a link between higher and lower regions of the central nervous system that coordinates the outputs of brain structures necessary for vocalization and other emotional behaviors.

De Lanerolle[29] reported that electrical stimulation of the ventrolateral pons (the pontine call site; PCS) also induced vocalization in unanesthetized, decerebrate cats. And it was reported that after a lesion was made in the region ventral to the medial lemniscus in the medulla, stimulation of the ipsilateral PCS no longer evoked vocalization.[30] Although these results suggested that the call sites rostral to the lower brain stem were located along the descending pathway from the midbrain to the medulla, there was no direct evidence to prove it. To trace the routes and destination of efferent fibers originating from the PAG, degeneration and axonal transport techniques have been used in a number of different species, including the cat[25,31,32] and the monkey.[33] These studies have demonstrated that the descending fibers from the PAG terminate in the nucleus retroambiguus,[32] wherein the caudal VRG expiratory neurons are located.

To trace the routes and destination of efferent fibers more precisely, injection of a small amount of the anterograde tracer PHA-L (*Phaseolus vulgaris* leukoagglutinin) was made into the PAG site in which electrical stimulation can induce vocalization.[34] At the level of the injection site, most labeled fibers passed laterally within the dorsal part of the midbrain tegmentum, in which the stimulus threshold for evoking vocalization was higher than that of the PAG. Further, there were some ipsilateral descending projections to the caudal part of the PAG and the lateral parabrachial nuclei. However, most labeled fibers passed ventrolaterally and consisted of a narrow bundle, corresponding to the PCS, in which the stimulus threshold for vocalization was the lowest. Descending fibers to the caudal medulla were identified by determining where electrical stimulation could induce vocalization. Along this descending pathway, labeled terminals were found in the dorsal nucleus of the lateral lemniscus, the nucleus retrofacialis, and the nucleus retroambigualis (Fig 1). Therefore, a small injection of anterograde tracer revealed a vocalization-specific pathway from the PAG, not only to the retroambigual nucleus, but also to the retrofacial nucleus, both of which contained high concentrations of respiratory neurons. The results suggested that stimulation of the PAG might directly send output to these respiratory neurons and modify their activities. Moreover, the results suggested that the respiratory neurons in the vicinity of the retrofacial nucleus also played an important role in controlling the coordinated activities of intrinsic laryngeal and respiratory muscles during vocalization.

Only recently has an attempt been made to make clear that caudal VRG expiratory neurons contribute to the control of intrinsic laryngeal and major respiratory muscles during vocalization.[35] During respiration, most of the caudal VRG neurons had an augmenting discharge pattern in phase with expiration. After the onset of the PAG stimulation, caudal

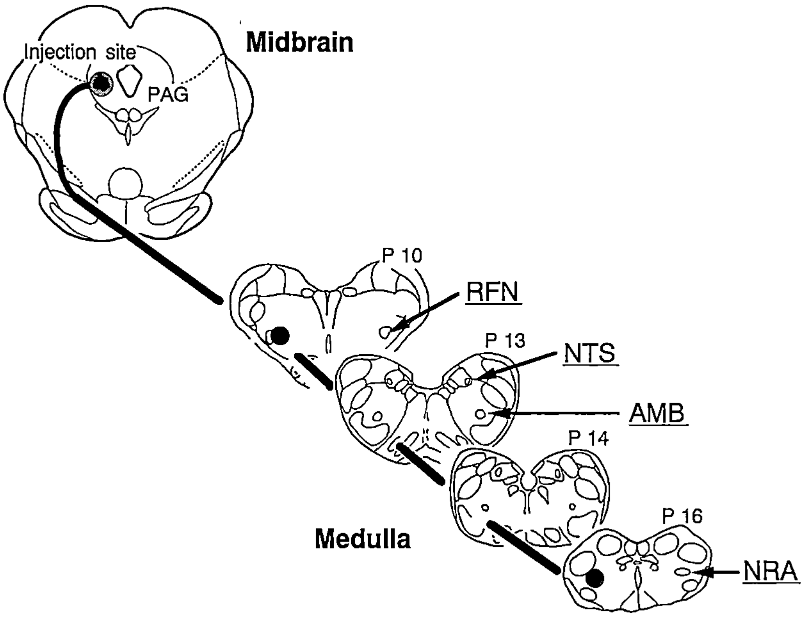


Fig 1. Schematic diagram of descending pathway from periaqueductal gray (PAG) to medullary respiratory neurons revealed by *Phaseolus vulgaris* leukoagglutinin injection. Descending fibers and projection sites are illustrated on frontal planes. Numbers indicate distance (millimeters) caudal to interauricular line. RFN — retrofacial nucleus, NTS — nucleus tractus solitarius, AMB — nucleus ambiguus, NRA — nucleus retroambigualis.

VRG neurons increased their firing rate to twice the rate found during expiration, in phase with the increased activity of the external oblique abdominal muscle, corresponding to the vocalization period. These results suggested that part of the activities of major expiratory muscles during vocalization might be controlled by the activities of caudal VRG expiratory neurons. However, behaviors of other respiratory neurons within the brain stem during vocalization are still uncertain.

MATERIALS AND METHODS

Surgical Preparation. The activities of various respiratory neurons within the brain stem were recorded during vocalization in 25 adult cats (2.5 to 4.5 kg) of both sexes. The surgical procedures, including precollicular-postmammillary decerebration, were performed under halothane–nitrous oxide anesthesia by way of intranasal intubation, which was then discontinued. Both carotid arteries were ligated. The animals were placed in a stereotaxic frame and supported with a rubber hammock and a clamp placed on an upper thoracic vertebra. The dorsal part of the occipital bone and the tentorium were removed to allow access to the brain stem by way of the intact cerebellum. Mean arterial blood pressure was monitored from the femoral artery. Rectal temperature was monitored and maintained at 36°C to 38°C with a radiant heating lamp. End-tidal carbon dioxide was monitored with an expired gas monitor and maintained between 3% and 5%.

Stimulation and Electromyography. Electromyograms were recorded from the laryngeal adductor muscle (thyroarytenoid; TA), laryngeal abductor muscle (posterior cricoarytenoid; PCA), diaphragm (DIA), and external oblique abdominal (EA) muscle. The electromyograms were recorded with a pair of thin (50 μm) stainless steel wires that were insulated except for about 1 mm at the tips and implanted into each muscle. They were amplified by a biophysical amplifier, high-pass-filtered with a 10-millisecond (ms) time constant, and monitored on an oscilloscope.

Vocalization was induced by electrical stimulation of the caudal part of the PAG according to the Horseley-Clark stereotaxic coordinates (A 1.0 to 2.5; L 1.0 to 2.0; H +2.0 to 0) with a tungsten microelectrode (shaft diameter of 250 μm, tip impedance of 5 to 10 MΩ; A-M Systems, Inc, Everett, Wash). The stimulus parameters were 20- to 80-μA rectangular pulses of 0.2-ms duration at a frequency of 100 Hz, lasting for 5 to 10 seconds.

Extracellular Recording of Respiratory Neurons. The activities of respiratory neurons were recorded extracellularly with tungsten microelectrodes (shaft diameter of 125 μm, tip impedance of 10 to 12 MΩ, FHC Co, Brunswick, Me). Single-cell activity was isolated with a time-amplitude window discriminator. The shape of the action potential that triggered the window discriminator was closely monitored on an oscilloscope at fast sweep speed (0.05 to 0.1 ms per division). Neurons were classified on the basis of the relationship of their firing patterns to the inspiratory activity of the DIA.

The projections of DRG inspiratory and BÖT augmenting expiratory neurons to the C4 spinal cord were tested by the use of collision between spontaneously occurring and antidromically evoked spikes.[36] Floating pin electrodes were inserted into the lateral

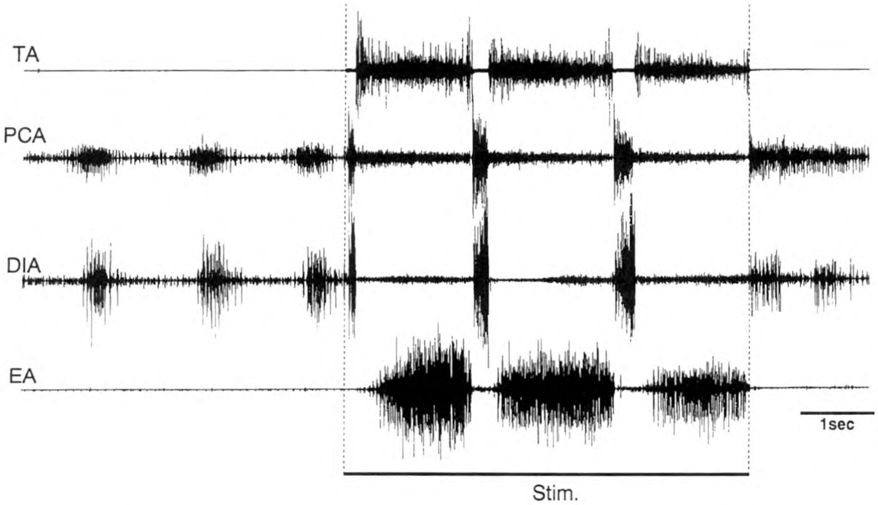


Fig 2. Electromyographic activities of intrinsic laryngeal and respiratory muscles during quiet respiration and PAG stimulation. TA — thyroarytenoid muscle, PCA — posterior cricoarytenoid muscle, DIA — diaphragm, EA — external oblique abdominal muscle.

and ventrolateral funiculi on both sides of the rostral C4 spinal cord. Cathodal current (0.2 ms, maximum 1 mA) was applied to the floating pin electrode. Rostral VRG respiratory neurons were identified as propriobulbar by their antidromic activation from the contralateral VRG or DRG, which was stimulated with a movable tungsten microelectrode (shaft diameter of 250 µm, tip impedance of 5 to 10 mΩ, A-M Systems, Inc). Moreover, these propriobulbar neurons were not antidromically activated by C4 spinal cord stimulation. To confirm that the recorded neurons were not laryngeal motoneurons, all recorded neurons were tested as to whether they were antidromically activated by ipsilateral recurrent laryngeal nerve stimulation with a bipolar cuff electrode.

Extracellular recordings, discriminated pulses, and electromyograms were stored on an FM magnetic tape recorder (DC-10 kHz; R-260, TEAC, Tokyo, Japan) for later analysis. Firing frequency histograms of recorded neurons were constructed by sampling discriminated pulses with a signal processor (7T18, NEC-Sanei, Tokyo). The peak firing rate of the recorded neuron in each respiratory cycle was calculated from the number of spikes within the 100-ms bin that had the maximum number of spikes in each respiratory cycle. During quiet breathing just before the onset of the PAG stimulation, peak firing rates for 5 cycles were employed as control values. The PAG stimulation, which lasted for 5 to 10 seconds, induced 3 to 7 periods of inspiration and vocalization, so the peak firing rates obtained from different stimulus trials (n of 4 to 6) were compared with control values. Possible differences were assessed with Mann-Whitney U tests.

Histologic Procedures. During the experiments, electrolytic lesions were made by passing 40 µA of anodal DC current for 20 seconds through the recording electrode to identify the location of selected neurons in the brain stem. At the end of the experiments, electrolytic lesions were also made in the PAG and the spinal cord. The portions of brain stem and spinal cord encompassing the electrode tracks and electrolytic lesions were fixed in 10% formalin. Tissue was sectioned at 50 µm and stained with cresyl violet. The locations of recorded neurons that were not marked by electrolytic lesions were estimated by the reading of the micromanipulator. The locations of the electrolytic lesions were referred to the stereotaxic atlases of Berman[37] and Snider and Niemer.[38]

RESULTS

Activities of Respiratory and Intrinsic Laryngeal Muscles During Vocalization Induced by PAG Stimulation. During quiet respiration, the PCA and DIA muscles discharged phasically and synchronously with the inspiratory phase, and no activities of TA and EA muscles were observed. After the onset of PAG stimulation, inspiration was always induced at first with an increase of the activities of the DIA and PCA muscles, regardless of when during the respiratory cycle PAG stimulation was applied.[39] Following the initial inspiration, vocalization and inspiration were induced alternately. The laryngeal adductor TA muscle was greatly recruited along with the EA muscle during vocalization, and the laryngeal abductor PCA muscle was recruited with the DIA during inspiration (Fig 2). These discharge patterns of the respiratory and intrinsic laryngeal muscles observed during PAG stimulation were well coordinated and totally different from those observed during respiration.

Changes in Firing Rates of DRG Inspiratory Neurons During Vocalization. Data were recorded from 16 DRG inspiratory neurons in the vicinity of the ventrolateral nucleus of the solitary tract, which were located 1 to 3 mm rostral to the obex and 1.5 to 2.5

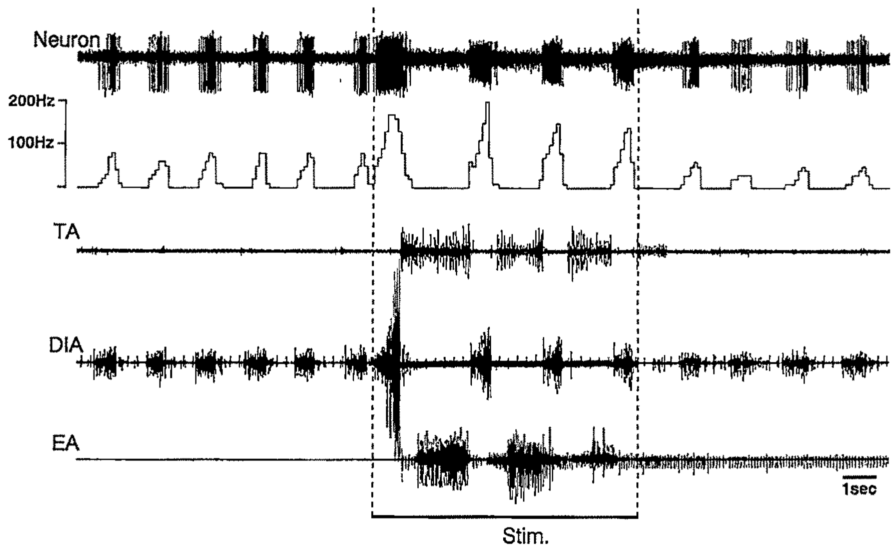


Fig 3. Changes in activities of inspiratory neurons in dorsal respiratory group during vocalization induced by PAG. Electromyograms were recorded from TA, DIA, and EA muscles.

mm lateral to the midline. Fifteen of 16 recorded neurons were activated antidromically by C4 spinal cord stimulation and categorized as bulbospinal inspiratory neurons. No recorded DRG neurons responded antidromically to stimulation of the ipsilateral recurrent laryngeal nerve. Conduction velocities for the 15 bulbospinal neurons ranged from 8 m/s to 48 m/s (29 ± 18 m/s; mean ± SD).

During the prestimulus respiration period, most of the recorded neurons (15/16) exhibited an augmenting discharge pattern in phase with the inspiratory phase (Fig 3). As shown in Fig 3, after the onset of the PAG stimulation, most of the recorded neurons (14/16) markedly increased their firing rate, up to 175% of their prestimulus level, throughout the whole stimulation period (see Table). After the end of stimulation, the firing rate of the neurons became rather smaller than that observed during the prestimulus period.

Changes in Firing Rates of Rostral VRG Respiratory Neurons During Vocalization. From the rostral VRG region, we recorded 40 propriobulbar respiratory neurons. According to their discharge patterns, these neurons were categorized as 10 I-Con neurons, 16 I-Dec neurons, and 14 E-Dec neurons. No recorded rostral VRG neurons responded to stimulation of the ipsilateral recurrent laryngeal nerve and spinal cord antidromically. Six I-Con, 10 I-Dec, and 6 E-Dec neurons were antidromically activated from stimulation delivered to the contralateral DRG or VRG regions.

BEHAVIORS OF BRAIN STEM RESPIRATORY NEURONS DURING PERIAQUEDUCTAL GRAY STIMULATION

Location	*Discharge Pattern*	*Recorded Cells*	*Increase*	*No Change*	*Decrease*
BÖT	E-Aug	24	2	2	20
Rostral VRG	I-Con	10	8	2	0
	I-Dec	16	2	6	8
	E-Dec	14	3	6	5
DRG	I-Aug	16	14	1	1

BÖT — Bötzinger complex; VRG — ventral respiratory group; DRG — dorsal respiratory group; E-Aug — augmenting expiratory neuron; I-Con — inspiratory neuron having constant discharge pattern; I-Dec — inspiratory neuron having decrementing pattern; E-Dec — expiratory neuron having decrementing pattern; I-Aug — augmenting inspiratory neuron.

Figure 4 shows the representative behavior of a propriobulbar I-Con neuron during vocalization. The I-Con neurons exhibited an increased firing rate during PAG stimulation in phase with the inspiratory phase. Eight of the 10 recorded I-Con neurons increased their firing rate, and the remaining 2 neurons did not change their firing rate during PAG stimulation (see Table).

During PAG stimulation, one half of the recorded I-Dec neurons (8/16) decreased their firing rate in phase with inspiration compared to their prestimulus period (Fig 5). Among the remaining 8 neurons, only 2 I-Dec neurons increased their firing rate. On the other hand, E-Dec neurons exhibited a variety of behavioral changes during PAG stimulation (Fig 6). Among the 14 recorded neurons, 3, 5, and 6 neurons, respectively increased, decreased, or did not change their firing rates (see Table).

Changes in Firing Rates of BÖT Expiratory Bulbospinal Neurons During Vocalization. Data were recorded from 24 BÖT expiratory neurons in the vicinity of the retrofacial nucleus, which were located 4 to 5.5 mm rostral to the obex and 3.5 to 5 mm lateral to the midline. Nineteen of the 24 recorded neurons were activated antidromically by C4 spinal cord stimulation and thus categorized as bulbospinal expira-

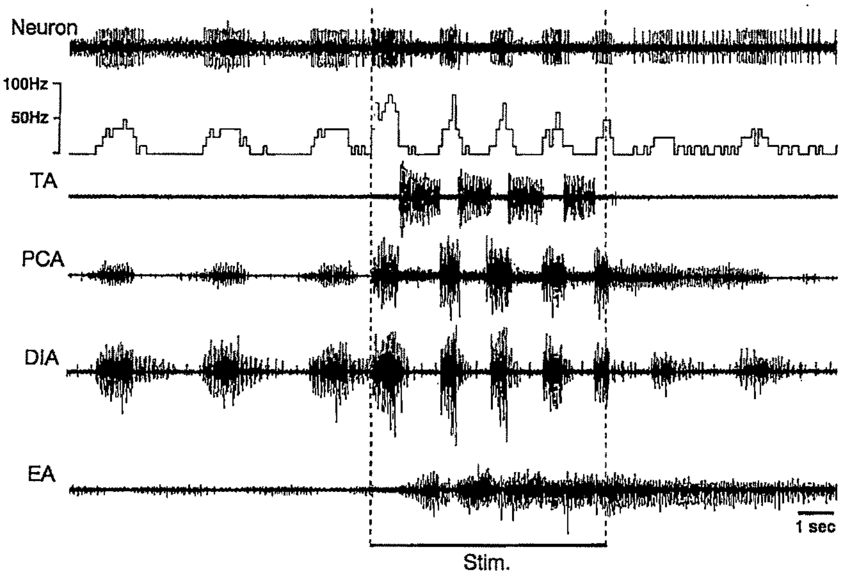


Fig 4. Changes in activities of inspiratory neurons with continuous discharge pattern in rostral ventral respiratory group (VRG) during vocalization induced by PAG. Electromyograms were recorded from TA, PCA, DIA, and EA muscles.

tory neurons. No recorded BÖT neuron responded to stimulation of the ipsilateral recurrent laryngeal nerve antidromically. Eight of 24 recorded neurons were antidromically activated by stimulation of the contralateral DRG. The conduction velocities for the 19 bulbospinal neurons ranged from 18 to 43 m/s (31.8 ± 11 m/s; mean ± SD).

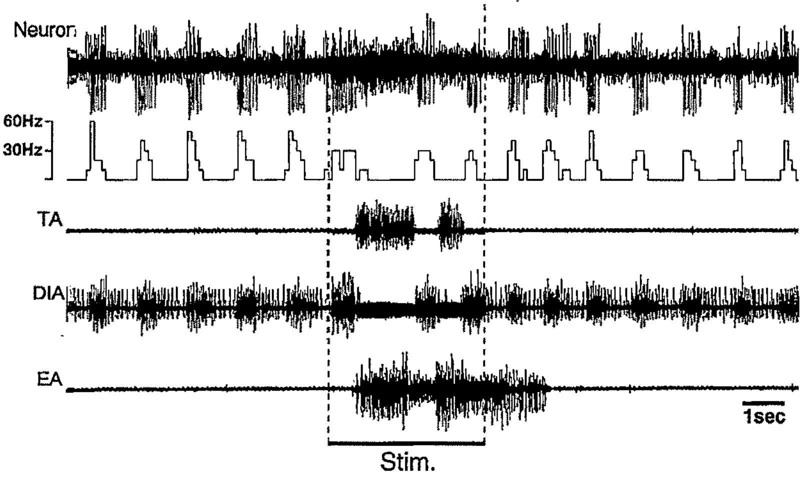
During the prestimulus period, every recorded neuron showed an augmenting discharge pattern synchronous with expiration (Fig 7). After the onset of PAG stimulation, the BÖT augmenting expiratory neurons suddenly ceased or greatly decreased their discharges. This suppression of the BÖT neurons was observed during the entire period of PAG stimulation; the firing rates of the neurons returned to their prestimulus level just after the cessation of stimulation. Twenty of the 24 recorded neurons ceased or greatly decreased their firing rate during PAG stimulation, and only 2 neurons increased their firing rate during stimulation (see Table).

Location of Neurons. Figure 8 shows the location of 5 I-Con, 7 I-Dec, 7 E-Dec, 9 BÖT augmenting expiratory, and 11 DRG inspiratory neurons. These neurons were obtained from 2 decerebrate cats. As shown in the horizontal plane (Fig 8A), BÖT augmenting expiratory and rostral VRG respiratory neurons were distributed from the level of the retrofacial nucleus to the rostral part of the nucleus ambiguus. There was some tendency for the expiratory neurons to be concentrated more rostrally than the inspiratory neurons. The DRG inspiratory neurons were distributed in and ventral to the nucleus tractus solitarius, as shown in Fig 8B,C.

DISCUSSION

This study investigated whether the coordinated activation of intrinsic laryngeal and respiratory muscles during vocalization is mediated via the central respiratory neurons that generate the pattern of motor output during respiration. The behavior of the caudal VRG expiratory neurons during vocalization has already been analyzed. Most of these neurons increased their firing rates during periods of vocali-

Fig 5. Changes in activities of inspiratory neurons with decrementing discharge pattern in rostral VRG during vocalization induced by PAG. Electromyograms were recorded from TA, DIA, and EA muscles.



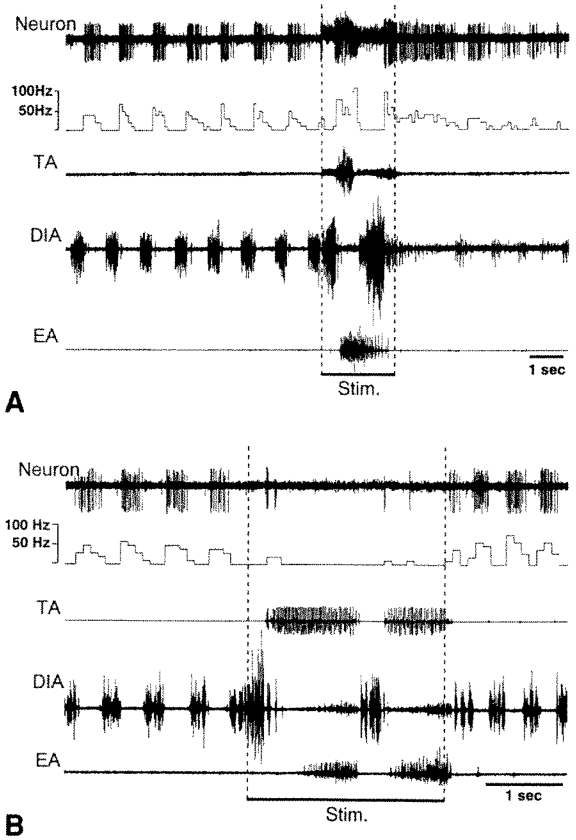


Fig 6. Changes in activities of expiratory neurons with decrementing discharge pattern in rostral VRG during vocalization induced by PAG. Electromyograms were recorded from TA, DIA, and EA muscles. A) Neuron that increased its firing rate during PAG stimulation. B) Neuron that decreased its firing rate during PAG stimulation.

zation synchronously with an increase of abdominal muscle activity.[35] This result suggested that the caudal VRG expiratory neurons may contribute to the generation of abdominal activity during vocalization.

The present study has extended the previous investigation of the role of central respiratory neurons in generating vocalization. In short, the main results are that during vocalization, 1) similar to the caudal VRG expiratory neurons, the activity of bulbospinal inspiratory neurons in the DRG and I-Con neurons in the rostral VRG was increased in phase with increased activity of the diaphragm during PAG stimulation; 2) I-Dec neurons decreased their firing rates during PAG stimulation; 3) 3 types of behavior of E-Dec neurons were observed (1 subset of neurons weakly fired and the second subset was active synchronously with the intrinsic laryngeal adductor and expiratory muscles, and the last subset did not change their firing rates compared to those during respiration); and 4) bulbospinal augmenting expiratory neurons in the BÖT either were silent or fired weakly during PAG stimulation.

Functional Significance of DRG Inspiratory Neurons During Vocalization. The firing of most inspiratory DRG neurons, which during respiration drive spinal inspiratory motoneurons,[7,8] was augmented in phase with inspiration during PAG stimulation in comparison to quiet respiration. During vocalization induced by PAG stimulation, in fact, it has been shown that the activities of the DIA and intrinsic laryngeal abductor were augmented. The firing of such neurons would presumably produce appropriate excitation of the inspiratory motoneurons of the spinal cord during PAG stimulation.

From the results obtained with a small injection of anterograde tracer, no direct pathway was revealed from the PAG to the DRG area, in contrast to PAG projections to the caudal VRG and BÖT complex areas.[34] However, DRG inspiratory neurons fired in a specific manner appropriate to produce vocalization, and this finding suggests that these neurons may receive motor commands from the PAG indirectly via other neural substrates.

Functional Significance of Rostral VRG Respira-

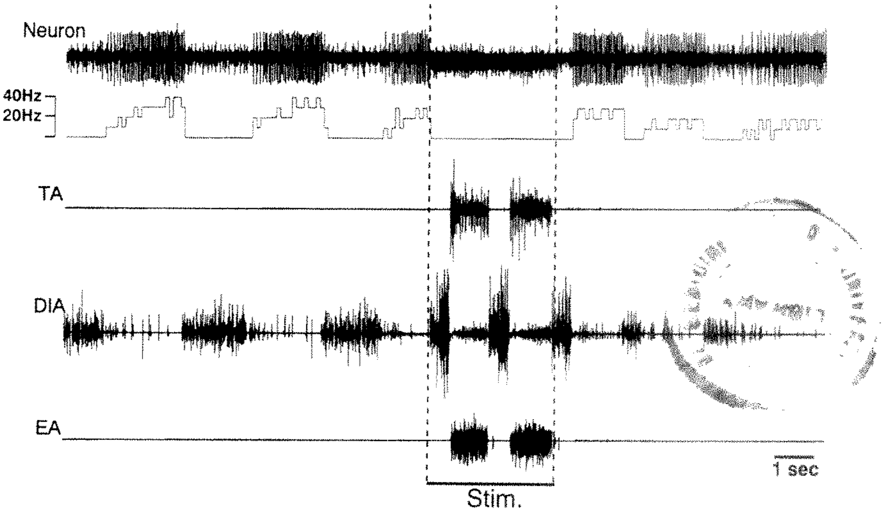


Fig 7. Changes in activities of augmenting expiratory neurons in Bötzinger complex during vocalization induced by PAG. Electromyograms were recorded from TA, DIA, and EA muscles.

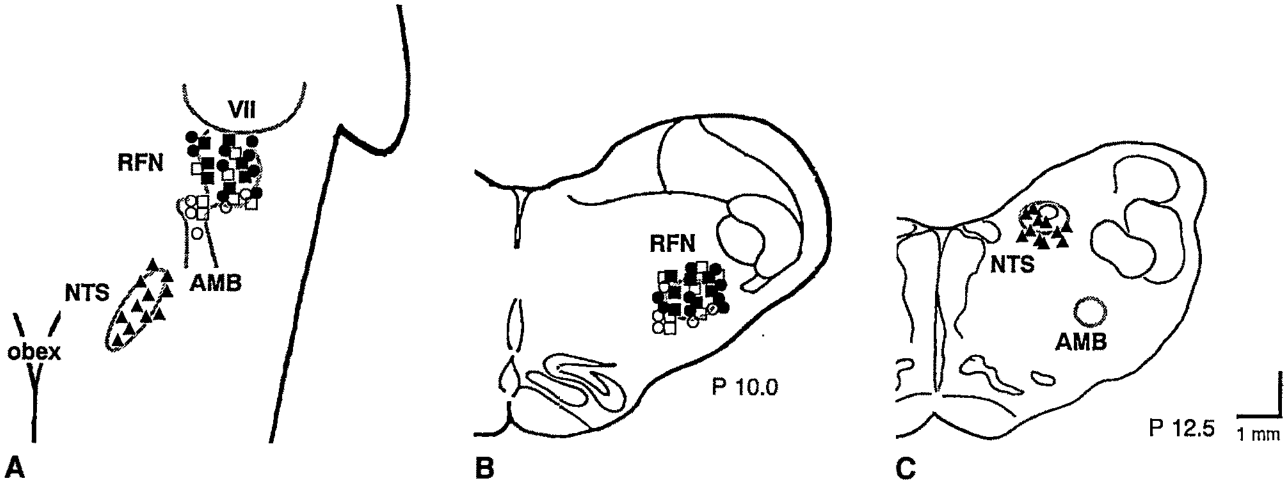


Fig 8. Distribution of augmenting inspiratory neurons in dorsal respiratory group (triangles) and inspiratory neurons with continuous discharge pattern (open circles), inspiratory neurons with decrementing discharge pattern (open squares), expiratory neurons with decrementing discharge pattern (closed squares), and augmenting expiratory neurons (closed circles) in Bötzinger complex projected onto A) horizontal and B,C) transverse planes. AMB — nucleus ambiguus, NTS — nucleus tractus solitarius, VII — facial nucleus, RFN — retrofacial nucleus, P 10.0, P 12.5 — distances (millimeters) caudal to interauricular line.

tory Neurons During Vocalization. In the present study, it was found that I-Con, I-Dec, and E-Dec neurons were not bulbospinal neurons and not motoneurons, by stimulation of the C4 spinal cord and the ipsilateral recurrent laryngeal nerve. The firing pattern alone is not enough to identify propriobulbar neurons, since motoneurons show a variety of firing patterns similar to those of propriobulbar respiratory neurons.[11,40] Consequently, respiratory neurons within the rostral VRG were identified as propriobulbar by antidromic excitation from the regions of the contralateral VRG and DRG. About half of these neurons (22 of 40) exhibited evidence of axonal branching in the contralateral VRG and DRG regions. This method of identifying propriobulbar neurons has a limitation; ie, it can miss real propriobulbar neurons that could not be activated by stimulation of a limited area of the VRG and DRG.

The firing of most I-Con neurons was augmented synchronously with inspiratory phases during PAG stimulation in comparison to respiration. Some I-Con neurons are known to be excitatory to inspiratory neurons of the DRG and VRG and vagal motoneurons with inspiratory activity.[11,41,42] Since DRG bulbospinal inspiratory neurons were active in phase with inspiration during PAG stimulation by way of unknown neural substrates, I-Con neurons may be one of the candidates for mediating excitation from the PAG to DRG inspiratory neurons. Moreover, such augmentation of I-Con activities during PAG stimulation would probably produce appropriate neuronal augmented activities of intrinsic laryngeal abductor motoneurons.

In contrast to I-Con neurons, half of the I-Dec neurons decreased their firing rates in phase with inspiration during PAG stimulation. It is known that I-Dec neurons monosynaptically inhibit inspiratory bulbospinal neurons in the DRG.[41] Therefore, it is plausible that such a suppression of I-Dec neurons may also produce the augmentation of DRG inspiratory neurons during PAG stimulation. However, it is known that I-Dec neurons also inhibit augmenting expiratory neurons in the BÖT and caudal VRG, although whether the same I-Dec neurons inhibit both inspiratory and expiratory neurons is not known.[11,42] Since 2 of the 16 recorded I-Dec neurons increased their firing rates during PAG stimulation, such increased activity might suppress the activity of caudal VRG expiratory neurons in phase with inspiration during PAG stimulation.

The E-Dec neurons are known to monosynaptically inhibit VRG inspiratory bulbospinal and propriobulbar neurons and vagal expiratory motoneurons and also to send axon collaterals to the BÖT and DRG.[12] In this study, E-Dec neurons showed a variety of behaviors during PAG stimulation. Some neurons increased their firing rates, some neurons did not change, and others decreased their rates during PAG stimulation. The functional significance of E-Dec neurons during vocalization has not been determined.

Functional Significance of BÖT Augmenting Expiratory Neurons During Vocalization. Most BÖT augmenting expiratory neurons became totally silent once PAG stimulation started or had only infrequent, sporadic firing during the entire period of stimulation. These augmenting expiratory neurons are known to connect inhibitory to phrenic[16] and intrinsic laryngeal adductor motoneurons,[11,14] and inspiratory neurons in the DRG[15] and VRG.[12,13] Therefore, PAG stimulation suppressed the inhibitory effects of the BÖT expiratory neurons on the inspiratory motoneurons and premotor neurons, which might induce the first inspiration just after the onset of stimulation. In other words, it is plausible that the conversion of respiration into vocalization may start by suppression of BÖT expiratory neurons. Moreover, the suppression of BÖT augmenting expiratory neurons would be in accord with the augmentation of the intrinsic laryngeal adductor muscles during vocalization.

Neuroanatomical experiments using a small injection of anterograde tracer revealed a direct pathway from the PAG to the BÖT complex area.[34] Since the suppression of the BÖT expiratory neurons was observed during the entire period of PAG stimulation, it is possible that such a projection from the PAG to the BÖT complex exerts a tonic inhibitory effect on the BÖT augmenting expiratory neurons. As mentioned previously, there is 1 other pathway from the PAG to the lower brain stem, that is, to the caudal VRG expiratory neurons. Since most of the caudal VRG neurons were augmented during PAG stimulation, the pathway from the PAG to the caudal VRG might exert an excitatory effect on the caudal VRG expiratory neurons. Therefore, the PAG has 2 opposite types of effect on the respiratory neurons within the lower brain stem.

Behaviors of Brain Stem Respiratory Neurons During Vocalization. The characteristic patterns of respiratory and intrinsic laryngeal muscles activated during vocalization, which are totally different from those occurring during respiration, are summarized as follows: 1) the inspiratory phase was induced at first just after the onset of PAG stimulation; 2) activities of DIA and EA were augmented in phase with inspiration and vocalization, respectively; and 3) activities of intrinsic abductor and adductor muscles were augmented in phase with inspiration and vocalization, respectively.

As mentioned above, most of the respiratory neurons within the brain stem are known to control the activities of the intrinsic laryngeal and respiratory muscles directly and/or indirectly to produce continuous respiration. In this study, we attempted to analyze whether these respiratory neurons contributed to produce the characteristic patterns of the muscles during PAG stimulation. It seems clear that the activities of some respiratory neurons during vocalization are adequate to explain the characteristic patterns of these muscles. For instance, BÖT augmenting expiratory neurons were extensively suppressed during PAG stimulation to produce the first inspiratory phase just after the onset of stimulation. To produce the enhanced activities of respiratory muscles, the firings of caudal VRG expiratory and DRG inspiratory neurons were augmented alternatively during the period of PAG stimulation. Moreover, I-Con neurons in the rostral VRG were augmented during the inspiratory phases of PAG stimulation to produce the enhanced activities of DRG inspiratory neurons. For producing the enhanced activities of intrinsic laryngeal muscles during PAG stimulation, the augmented firing of I-Con neurons in the rostral VRG during the inspiratory phase and the suppressed firing of BÖT augmenting expiratory neurons during vocalization may contribute.

Electrical stimulation to the PAG activated the neurons that sent excitatory and inhibitory outputs from the PAG to the brain stem respiratory neurons. These motor commands from the PAG modified the firing patterns of a part of the respiratory neurons adequately to produce the characteristic coordinated patterns of the major respiratory and intrinsic laryngeal muscles during vocalization. This modification may include the conversion from involuntary respiration to voluntary vocalization. However, the excitatory sources of caudal VRG expiratory neurons during vocalization are still uncertain. Katada et al[35] defined nonrespiratory neurons in the vicinity of the nucleus retroambiguus that were recruited and activated in phase with vocalization during PAG stimulation. Such neurons were not activated by L1 spinal cord stimulation, but were orthodromically activated by the trained stimulation of the PAG. Although the projection sites of these neurons are unknown, such neurons could be one of the candidates for excitatory sources of caudal VRG expiratory neurons. A more complete understanding of the possible role of respiratory and nonrespiratory neurons in controlling respiratory and intrinsic laryngeal muscles during vocalization must await further elaboration.

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SUPPLEMENT 179 — SEPTEMBER 1999
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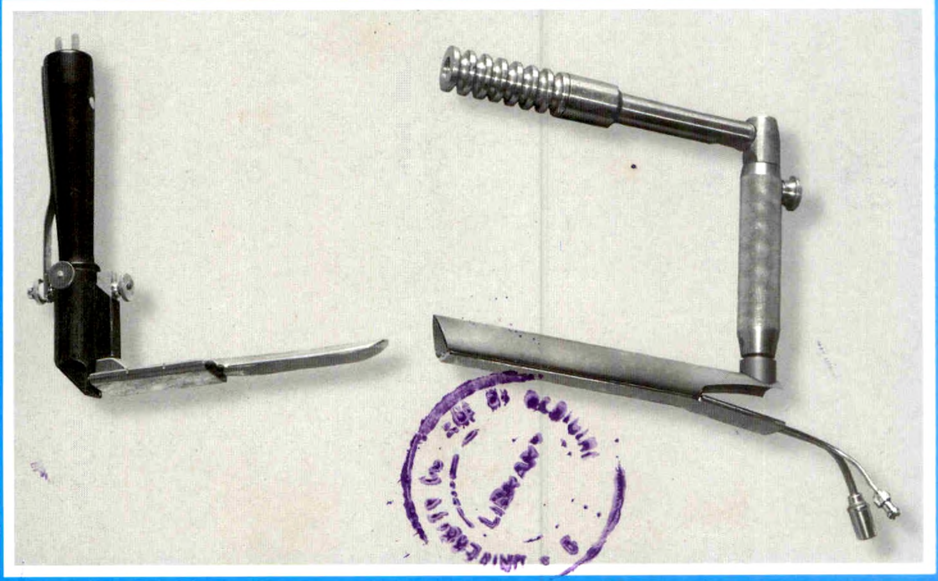
UNIVERSAL MODULAR GLOTTISCOPE SYSTEM: THE EVOLUTION OF A CENTURY OF DESIGN AND TECHNIQUE FOR DIRECT LARYNGOSCOPY

STEVEN M. ZEITELS, MD, FACS



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UNIVERSAL MODULAR GLOTTISCOPE SYSTEM: THE EVOLUTION OF A CENTURY OF DESIGN AND TECHNIQUE FOR DIRECT LARYNGOSCOPY

STEVEN M. ZEITELS, MD, FACS

This work is dedicated to Charles W. Vaughan, MD, who in the spirit of
Chevalier Jackson conferred to his students the art, craft, and science
of rigid endoscopy of the upper aerodigestive tract.

COVER PHOTOGRAPH — Left: Kirstein Autoscope, 1895. Right: Universal Modular Glottiscope, 1999 (Endocraft® LLC, Boston, Mass; US patent 5,893,830).

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UNIVERSAL MODULAR GLOTTISCOPE SYSTEM: THE EVOLUTION OF A CENTURY OF DESIGN AND TECHNIQUE FOR DIRECT LARYNGOSCOPY

STEVEN M. ZEITELS, MD, FACS
BOSTON, MASSACHUSETTS

Since Kirstein introduced formal direct examination (autoscopy) of the glottis in 1895, a great number of laryngoscopes have been produced to view the vocal folds; however, none have had universal appeal. The primary goals for the designs have been to optimize exposure and to facilitate instrumentation of the glottis. An analysis of more than 50 laryngoscopes was done to assess key design characteristics that would ideally be present in a laryngoscope for optimally viewing the musculomembranous vocal folds. The Pro/Engineer and Pro/Mechanica computer programs were used to model the universal modular glottiscope. This new laryngoscope comprises a plurality of specially designed examining tubes that are bivalved proximally to improve utilization of hand instrumentation, and form a single tube distally to achieve internal distention of the supraglottal tissues. The distal lumen has an arcuate isosceles-triangular conformation to optimally expose the glottis. The base of the tube is detachable for the difficult intubation or the placement of bronchoscopes. The examining tubes vary in size and dimension to accommodate the diversity of human anatomy. The tubes are easily attachable to and detachable from an ergodynamically designed universal handle that can be joined to fulcrum laryngoscope holders or suspension gallows. The universal modular glottiscope evolved from the selective integration of optimal 20th-century design modifications of Kirstein's original autoscope. This new laryngoscope is ideally suited for phonomicrosurgery as well as for difficult intubation.

KEY WORDS — direct laryngoscopy, laryngoscope, microlaryngoscopy, microsurgery, phonomicrosurgery, phonosurgery, vocal cords, vocal folds.

INTRODUCTION

The sesquicentennial of Horace Green's[1] description of direct laryngoscopy and the centennial of Alfred Kirstein's[2,3] introduction of the direct laryngoscope passed recently. With the closure of the 20th century and the expansion of minimally invasive surgical technology, it is a propitious time to assess our past experience with direct laryngoscopy to prepare for future developments in endolaryngeal surgery. Optimally designed direct laryngoscopes can facilitate the new generation of phonomicrosurgical procedures. Strategies for these operations have been catalyzed by the essential need for a healthy voice in our communication-based society.

During the past century, direct laryngoscopy and its associated instrumentation have evolved along two major pathways. The initial and ever-present purpose of a rigid laryngoscope is to provide an effective endoscopic pathway to diagnose and treat disorders of the larynx. However, even greater significance can be attributed to direct laryngoscopic endotracheal catheterization (intubation).[4-8] This procedure was introduced as an outgrowth of Jackson's[9,10] work at the beginning of the 20th century, and was used at that time during "sanguinary" endoscopic procedures of the aryepiglottic fold.[11] Today, endotracheal anesthesia has become a fundamental component of cardiopulmonary resuscitation and general anesthesia.

These two purposes for direct laryngoscopy (endolaryngeal surgery and endotracheal intubation) have had divergent pathways of technical design. However, initiatives in instrument development for both applications sought to improve exposure and/or instrumental manipulation of the larynx, and most frequently, the glottis. Ironically, there seems to be little communication about laryngoscopy between anesthesiologists and laryngologists until they mutually converge on a difficult airway. Therefore, an analysis was done of over 50 direct laryngoscopes with the hope of isolating the key design features, which could be incorporated into one laryngoscope that might serve both disciplines. This resulted in the universal modular (UM) glottiscope system (Endocraft® LLC, Boston, Mass; US patent 5,893,830).

The work herein is the first highly detailed analysis of (surgical) direct laryngoscope design since Jackson's discussion of the subject in 1915,[12] and incorporates a majority of the subsequent 80 years of innovations. The qualitative nature of the instru-

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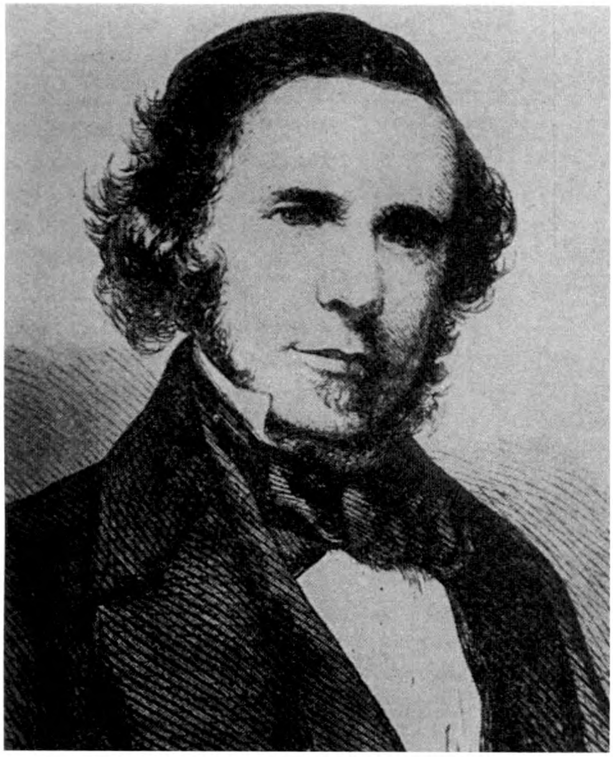

Fig 1. Horace Green: father of American laryngology.

ment analysis reflects the fact that the introduction and marketing of prior instruments lacked strict adherence to the scientific method. This occurred because surgical laryngoscopy and phonomicrosurgery are an art and a craft as well as a surgical science. Although this investigation similarly consists of a subjective assessment of the UM glottiscope in the context of over 50 other laryngoscopes, a prospective protocol for evaluating the UM glottiscope is in progress and will be reported after 250 cases.

The reader is encouraged to review the original references to better understand the pattern of laryngoscopic development, since this work serves as the author's perspective of the last century of progress. The multitude of images are intended to illustrate the principles of direct laryngoscopy and to serve as a resource for students of laryngoscopy, who are unable to access many of the original instruments.

BACKGROUND AND HISTORY

Horace Green (1802-1866). Direct visualization of the laryngeal introitus was reported first by Green (Fig 1), in his seminal text entitled "On the Surgical Treatment of Polypi of the Larynx, and Oedema of the Glottis." Green was managing an 11-year-old girl with obstructive sleep apnea and initially removed her tonsils to treat the symptomatology. That intervention was unsuccessful, and over time her obstructive stridulous symptoms worsened.

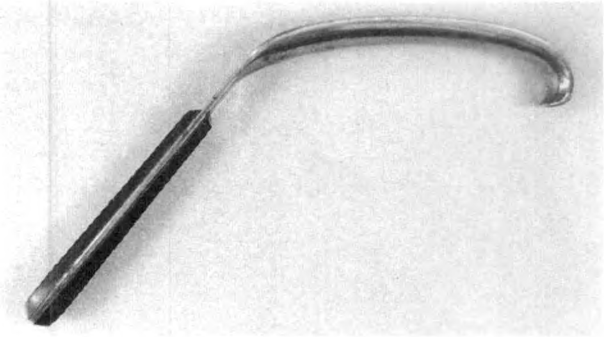

Fig 2. Nineteenth-century bent-tongue spatula. Note distal curve designed to engage vallecula glosso-epiglottica. (Courtesy of Massachusetts Eye and Ear Infirmary.)

Green suspected a laryngeal problem and employed a bent-tongue spatula, similar to a Macintosh spatula laryngoscope (Fig 2), to examine the lower pharynx and larynx, whereupon he noted a fibroepithelial polyp that was ball-valving into the glottal aperture. Because laryngotomy (laryngofissure) had been described and successfully achieved in only 1 adult patient,[13] Green pursued a transoral excision of the mass. Under direct vision, using sunlight for illumination, he removed the polyp and cured the apnea. "I succeeded in catching the hooks into the top of the tumour, and turning quickly the blade of the knife downwards, passed it over the left border of the glottis, I cut from behind forewords, and hap-

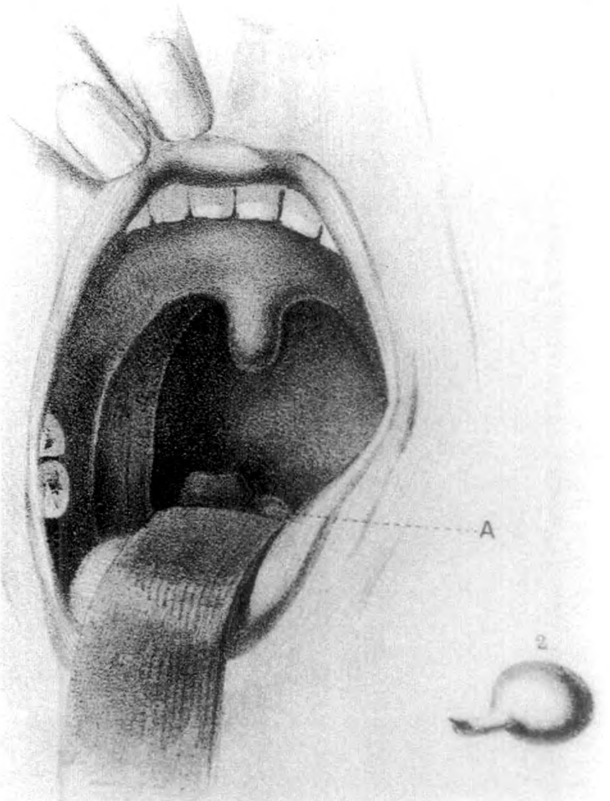

Fig 3. Laryngeal polyp excised under direct vision. Green explained that this was artist's rendition of what was seen from behind Green.[1]

pily, dividing the pedicle near its attachment, brought the entire tumour out of the larynx"[1(p64)] (Fig 3[1]). Until 1995,[14] all prior historical accounts had credited Kirstein with performing the first direct laryngoscopy. This oversight probably occurred because Green had done his work prior to the existence of the field of laryngology.

Green had studied for several months in Europe in 1838[15] and claimed to be unaware[16] of the work in airway diseases by Trousseau and Belloc.[17] Subsequently, he returned to New York City, resumed his medical practice, and developed a keen interest in throat and upper aerodigestive tract disease of infectious causation.[1,18-22] Green became the first airway disease specialist in the United States and the first laryngologist,[23] as laryngology had yet to exist as a specialty. He boldly, and at times successfully, treated patients by means of transoral application of caustics for infectious obstruction of the air passages. Since his endolaryngeal techniques could not be reproduced, his integrity was brought into question. There were even unfounded accusations that Green had taken credit for accomplishments of Trousseau and Belloc.[15] Ultimately, Green was vindicated prior to his death by the development of laryngology[24-27] and mirror-guided procedures that were similar in nature to those he had performed over a decade earlier.[28-30] Elsberg dedicated the first meeting of the American Laryngological Association to Green's pioneering efforts.[23]

Alfred Kirstein (1863-1922). It appears that Kirstein[2,3] (Fig 4[12]) was unaware of Green's work when he reintroduced direct laryngoscopy about 50 years subsequent to Green. Kirstein carefully reported his technique and instrumentation, detailing the ideal head and neck position (sniffing) as well as the vector forces required for successful laryngeal exposure. He was in private practice (personal communication, 1997, H. von Leden) and was well aware of potential resistance to his new technique, which represented a dramatic paradigm shift from the prior 35 years of mirror laryngoscopic surgical management. Since the laryngoscope was synonymous with the laryngeal mirror, he carefully named his method "autoscopy" to avoid controversy. Throughout his monograph, Kirstein referred to autoscopy as a significant innovation in the armamentarium of the laryngologist, rather than a replacement for mirror examination.

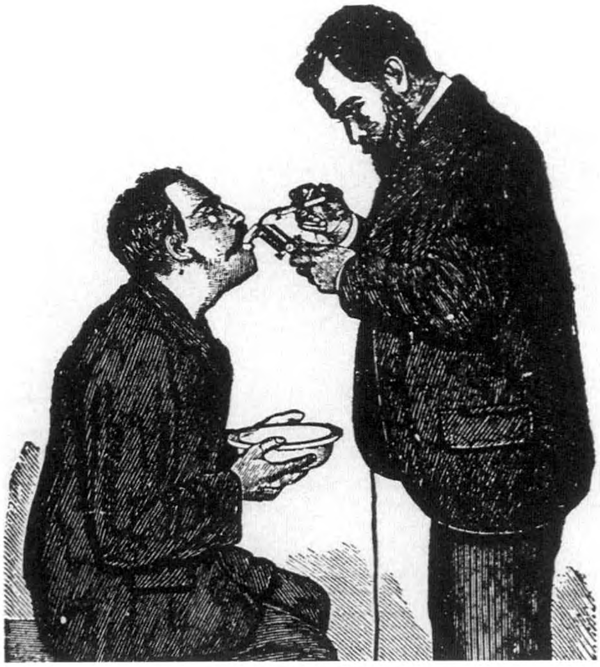

Fig 4. Kirstein performing direct laryngoscopy with patient in sniffing position. (From Jackson.[12])

Kirstein displayed cautious confidence and keen perception when he stated in the preface of his monograph, "Of course, many a laryngologist is convinced that the laryngological technique needs no additions; others may think differently. Only the future can decide this question."[31(pVII)] Furthermore, of his 7 conclusions, the only italicized one stated, "In endolaryngeal and endotracheal surgery, autoscopy will take the front rank as the standard method; of course within its anatomic limits."[31(p57)] Kirstein even foresaw the heuristic value of direct examination of the vocal folds, when he predicted that magnification and stroboscopy[32,33] would be joined with autoscopy.

Kirstein's original spatula-laryngoscope was similar to a tongue spatula (Fig 2) and required the headlight that he designed (Fig 5). His electrified autoscope (Fig 6) had all of the fundamental elements of a modern rigid laryngoscope: 1) a spatula blade to distract the supralaryngeal or supraglottal tissues away from the laryngeal introitus, 2) self-contained illumination in the form of an electric-powered bulb (Fig 7; the proximal illumination was reflected dis-

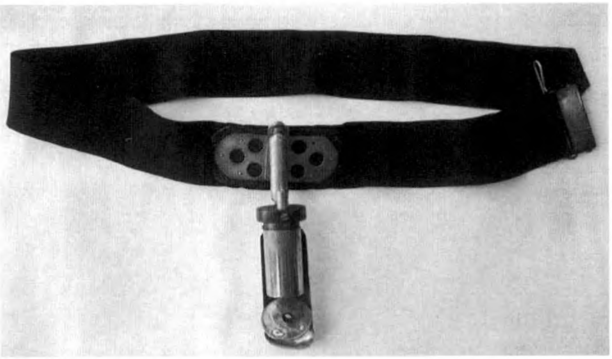

Fig 5. Kirstein headlight. (Courtesy of Massachusetts Eye and Ear Infirmary.)

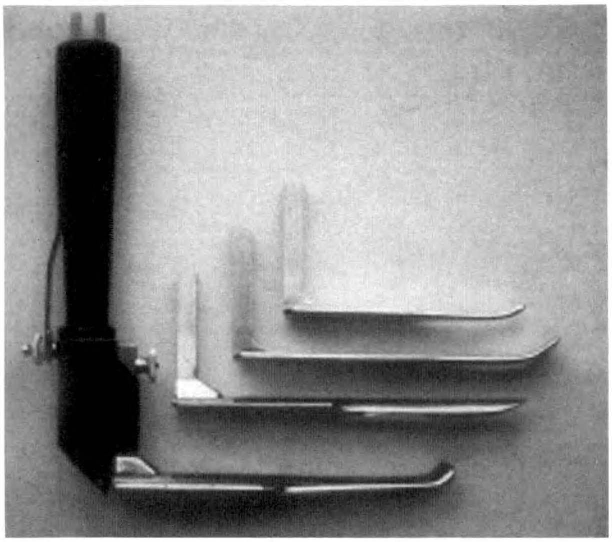

Fig 6. Kirstein autoscope. Note variety of detachable blades and universal handle. (Collection of S. Zeitels; gift from M. S. Strong.)

tally by means of a prism), and 3) a sturdy universal handle, which could be attached to a number of spatula blades. The valuable concept of a universal handle has mostly been ignored in present-day surgical instrumentation.

Early 20th-Century Laryngoscope Design: Gustav Killian and Chevalier Jackson. Kirstein had experimented with spatula and tubular laryngoscope blades, and all direct rigid laryngoscopes derive from these initial investigations. Gustav Killian (1860-1921; Fig 8) recounted that he mistrusted the veracity of Kir-

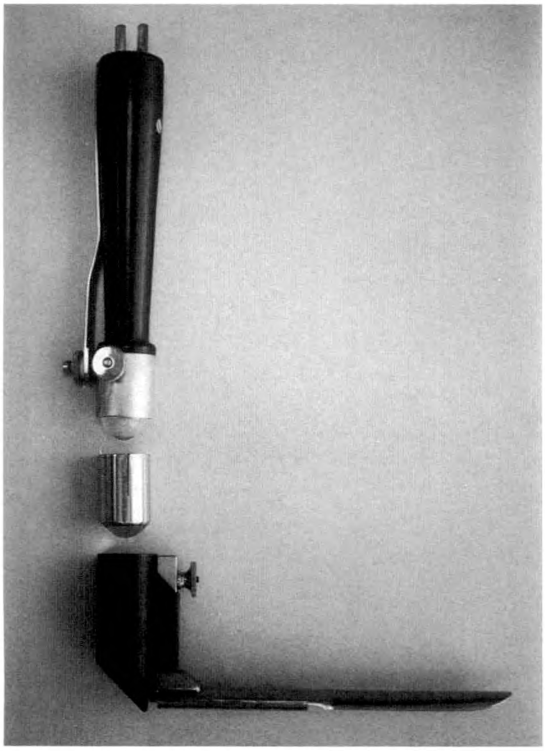

Fig 7. Kirstein autoscope. Universal handle is separated to display bulb illumination. (Collection of S. Zeitels; gift from M. S. Strong.)

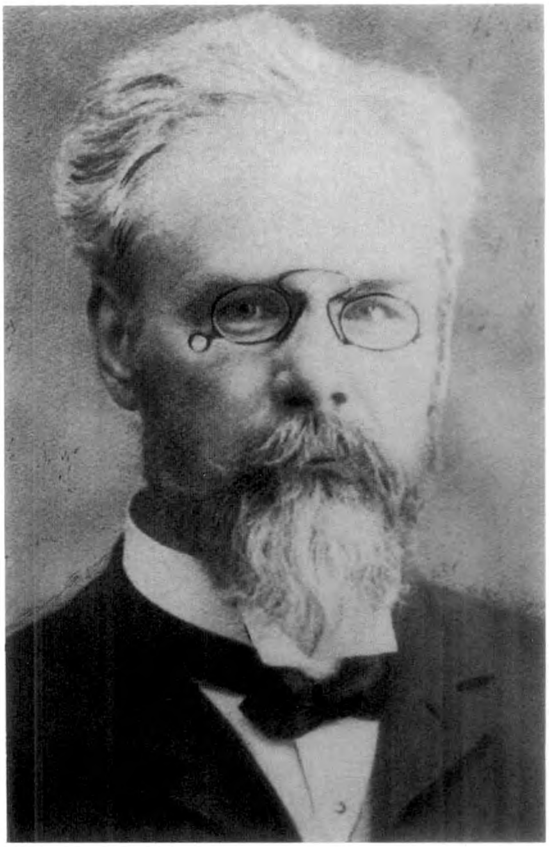

Fig 8. Gustav Killian. (Courtesy of Massachusetts Eye and Ear Infirmary.)

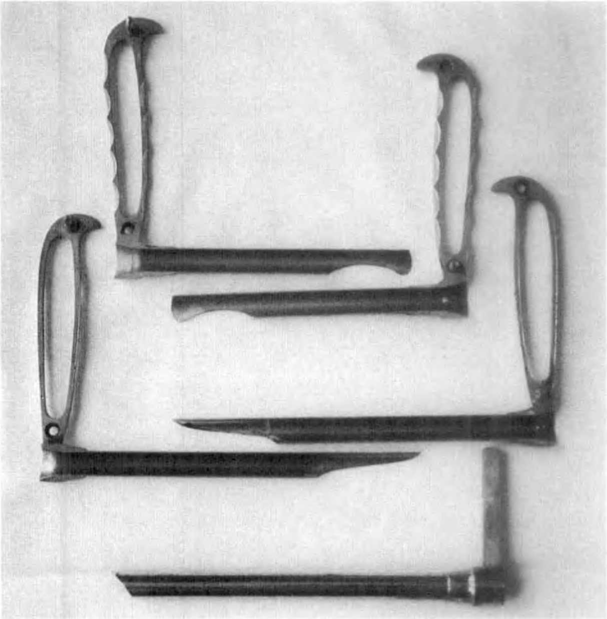

Fig 9. Killian laryngoscope tubes. Upper two tubes separate in sagittal plane to facilitate placement of bronchoscopes. (Courtesy of Massachusetts Eye and Ear Infirmary.)

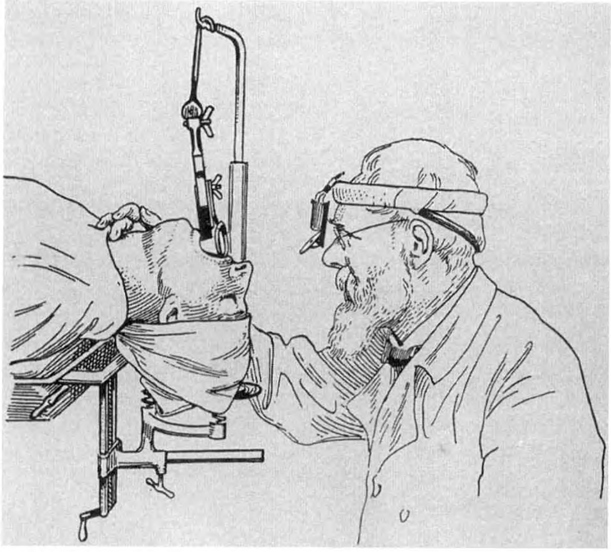

Fig 10. Killian performing suspension laryngoscopy. Patient is extended both in cervical spine as well as at atlanto-occipital joint, and Killian is applying external counterpressure to improve exposure. (From Killian.[38])

stein's report until he witnessed Kirstein demonstrating the direct laryngoscopic technique. Killian stated, "From that time, my entire thought became bound up in the subject."[34] He became intensely interested in endoscopy, perfected rigid bronchoscopy[35] shortly thereafter, and designed a number of tubular direct-laryngoscope blades (Fig 9). Among them was a separating laryngoscope, which was used to facilitate placement of a bronchoscope (Fig 9). Killian soon introduced the concept of an inverted V spatula blade,[36] which conformed to the anterior glottal commissure. This idea had been omitted from the design of most tubular laryngoscopes. Killian conceived laryngeal suspension in 1910[34] while hanging a cadaver by a spatula for his artist to draw endolaryngeal anatomy. He reported[37] on the new laryngoscope and associated suspension gallows (Fig 10[38]) in 1912, and later assimilated the inverted V spatula (Fig 11[38]) into his invention.

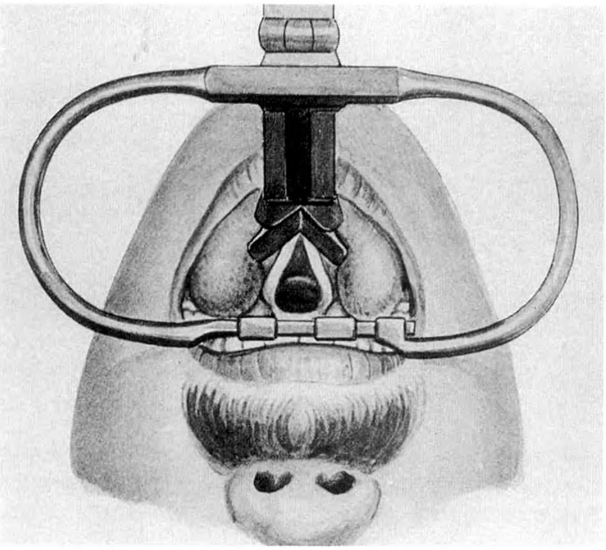

Fig 11. Killian's inverted V spatula blade joined to his suspension laryngoscope. (From Killian.[38])

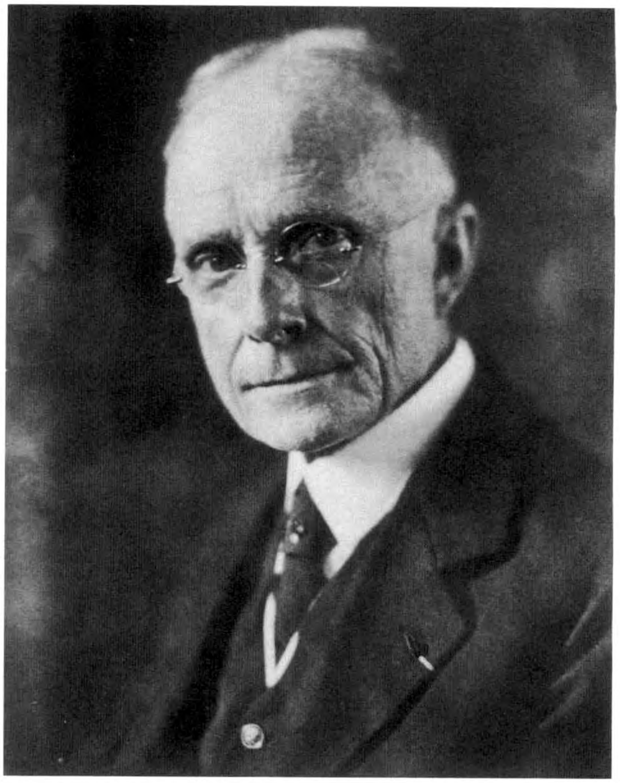

Fig 12. Chevalier Jackson. (Courtesy of College of Physicians of Philadelphia.)

Chevalier Jackson (1865-1958; Fig 12) was inspired by Killian's work, and Jackson's contributions to direct laryngoscopy have been detailed in a prior

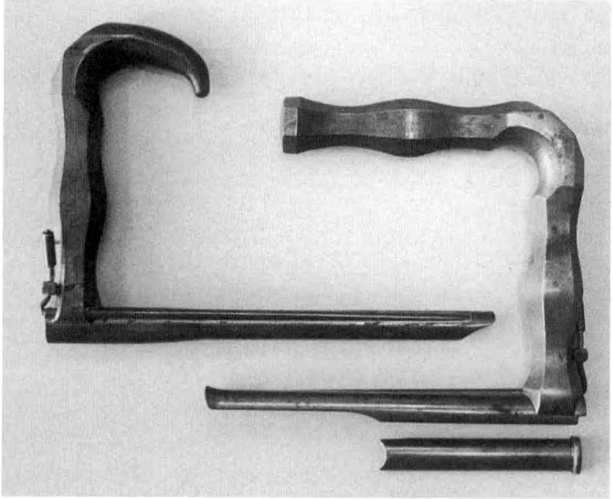

Fig 13. Two early 20th-century Jackson laryngoscopes with improved ergodynamic handles. Right laryngoscope has detachable bottom to facilitate bronchoscope placement. Note light carriers, which provided distal illumination. (Collection of S. Zeitels.)

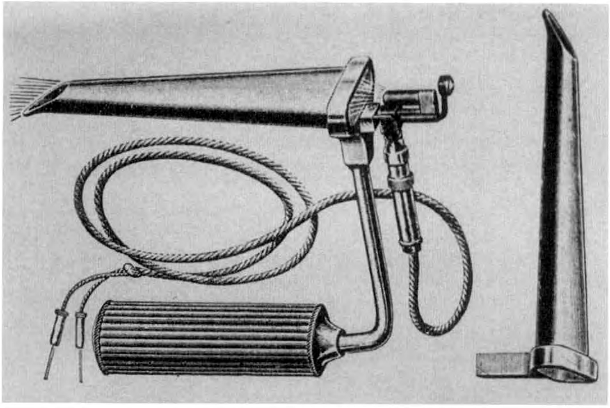

Fig 14. Yankauer's tube laryngoscope had wide proximal lumen and was first binocular tubular laryngoscope. (From Jackson.[12])

manuscript.[39] He authored the first textbook of rigid endoscopy of the upper aerodigestive tract in 1907[9] and dedicated that work to Killian. Jackson introduced the concept of a C-shaped handle[9] instead of the conventional one configured as an L, which facilitated a more appropriate manual vector for applying force to distract the supraglottal tissues. Soon thereafter, the contours of the handle were adjusted more ergodynamically (Fig 13) for manual comfort.[40] That handle design is still present in a great number of current-day laryngoscopes.

Jackson also introduced 3 other tremendously important design features. He altered Killian's idea for sagittally splitting the entire laryngoscope, so that only the bottom of the examining tube was detachable (Fig 13).[9] This laryngoscope was an excellent diagnostic instrument, because its shape as a tube proximally and a spatula distally greatly facilitated placement of rigid bronchoscopes. Jackson introduced distal illumination,[9] which has become a fundamental component of almost all current laryngoscopes. Finally, Jackson, Tucker, and Clerf[41] introduced the laryngostat, which incorporated the inverted V shape into a tubular laryngoscope to conform to the anterior glottal commissure. The distal lumen of this laryngoscope was teardrop-shaped to preclude vestibular fold overclosure[41] during surgery on the musculomembranous vocal folds. Distraction of the supraglottal soft tissues to enhance exposure of the vocal folds is currently referred to as internal distention.[42]

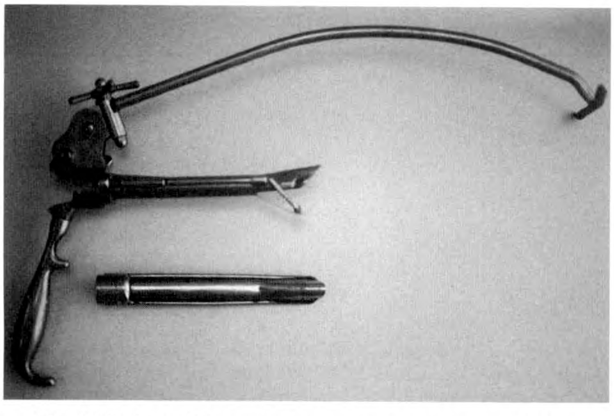

Fig 15. Roberts' binocular laryngoscope system with detachable tubes. Tube that is attached to handle has distal internal distention mechanism for hinged base. (Collection of S. Zeitels; gift from V. Calcaterra.)

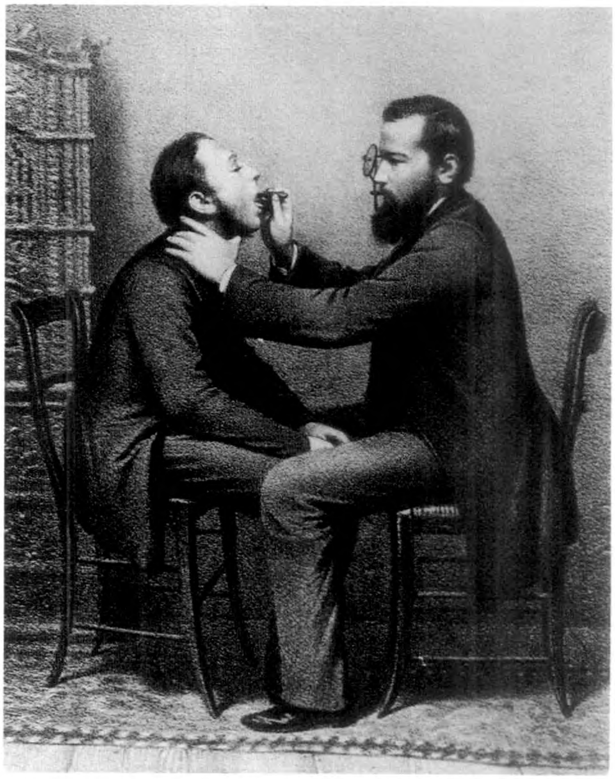

Fig 16. Czermak performing indirect laryngoscopy. Note that he is applying external counterpressure and that patient is in sniffing position. (From Der Kehlkopfspiegel und seine Verwerthung fur Physiologia und Medizin.)

Binocular Laryngoscope Tubes. At the turn of the century, Yankauer was apparently the first to design a binocular laryngoscope tube[43] (Fig 14[12]). One is on display in the Wood Library Museum of the American Society of Anesthesiologists. Approximately 40 years later, Roberts and Forman[44,45] described a novel laryngoscope that had detachable binocular tubes (Fig 15). These instruments were introduced prior to the era of microlaryngoscopy, which required larger-diameter tubes to accommodate the microscope oculars. Kleinsasser[46] and Jako[47,48] shouldered the development of current binocular laryngoscope tubes that are compatible with the surgical microscope. However, there is an ever-present limitation on widening the diameter of the examining tube, since increasing its size restricts placement of the laryngoscope.

Patient Position. Czermak[24,25] introduced the sniff-

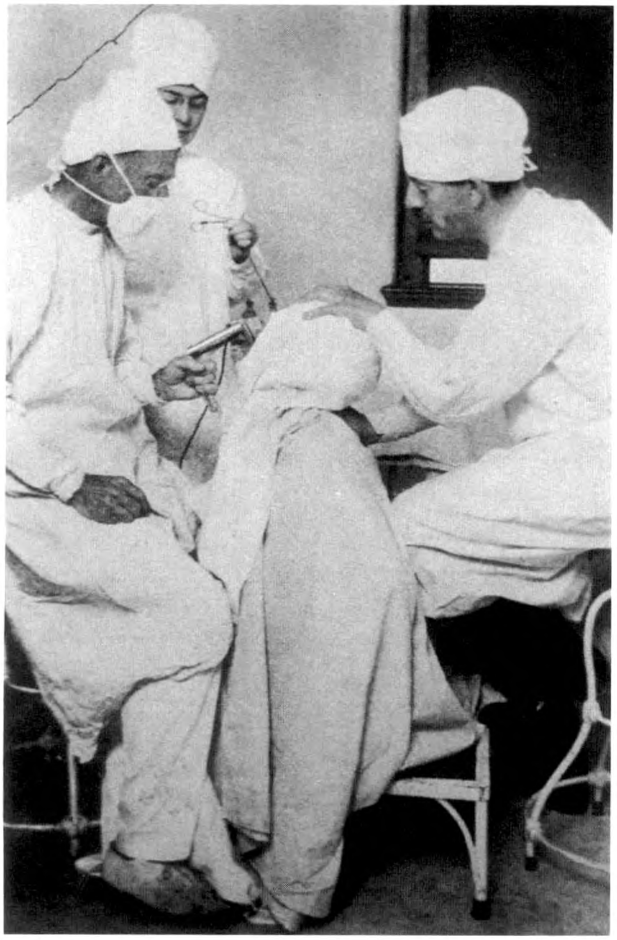

Fig 17. Jackson performing sitting direct laryngoscopy. Again, note sniffing position. (From Jackson.[12])

ing position while perfecting mirror laryngoscopy (Fig 16). Kirstein adopted the same position for sitting direct laryngoscopy (Fig 4). It comprised flexion of the cervical spine in relation to the thoracic spine and extension of the head at the atlanto-occipital joint. Jackson demonstrated that this position (Fig 17[12]) could be achieved in a supine patient (Fig 18) with an assistant supporting the patient's head and neck (Boyce-Jackson position; Fig 19). When surgeons attempt to simulate the Boyce-Jackson position without an assistant by placing a pillow under the vertex, extension at the atlanto-occipital joint can actually be impaired, thus inhibiting proper positioning.

On the basis of Jackson's work, anesthesiologists employed the Boyce-Jackson position for endotracheal intubation.[4-8] Recently, this precept was challenged in a study[49] that examined the efficacy of 3 head and neck positions for exposing the glottis with different-sized tubular laryngoscopes: 1) extension of the head and neck, 2) (sniffing) extension of the head and flexion of the neck, and 3) flexion of the head and neck.

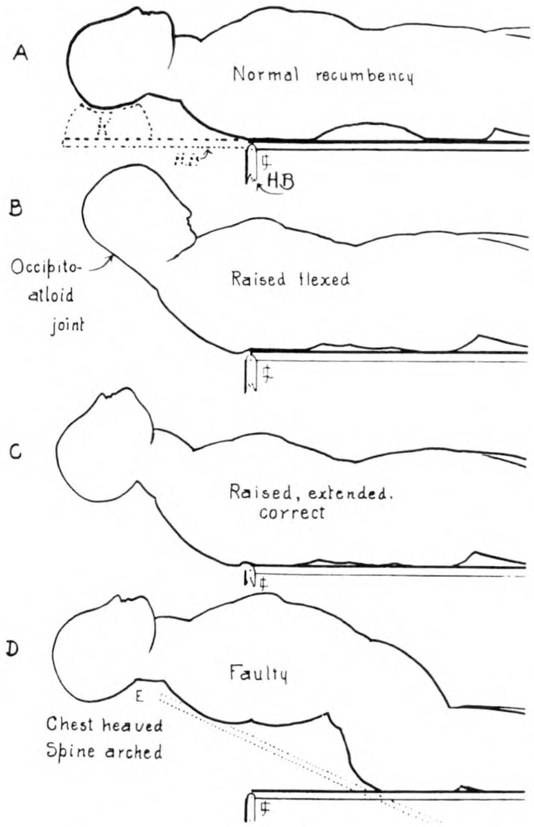

Fig 18. Jackson's comparison of various head and neck positions for direct laryngoscopy. (From C. Jackson and C. L. Jackson. Bronchoscopy, esophagoscopy, and gastroscopy. 3rd ed. Philadelphia, Pa: WB Saunders, 1934: 90.)

Although the head-forward flexion-flexion position was described by Killian (cited in Bruck[50]) for difficult indirect laryngoscopy (Fig 20[50]), and Johnston[51] for difficult sitting direct laryngoscopy, the sniffing position has been accepted as the ideal configuration for examination of the larynx. As had been

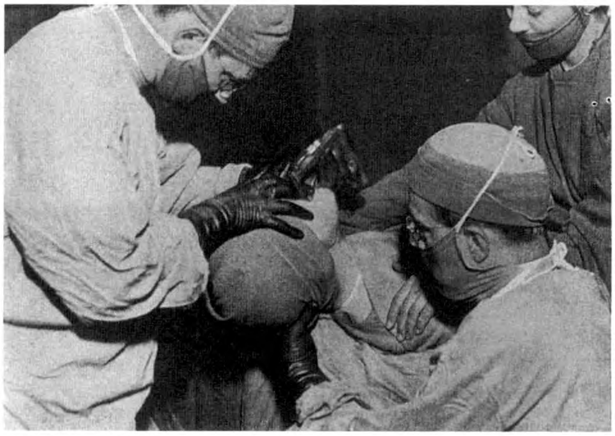

Fig 19. Assistant is placing patient in Boyce-Jackson position for supine direct laryngoscopy. Without general anesthesia, both surgeon and patient are mobile to facilitate optimal optical pathway. (From C. Jackson and C. L. Jackson. Diseases of the nose and throat. Philadelphia, Pa: WB Saunders, 1945:435.)

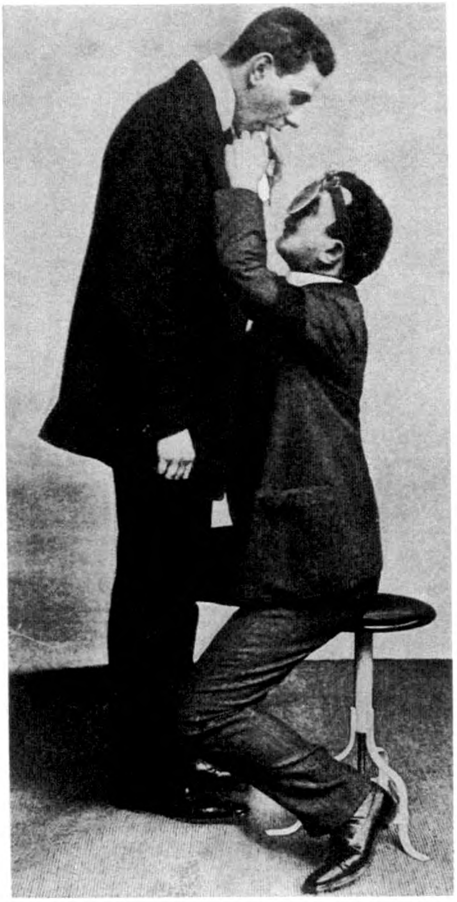

Fig 20. Killian's flexion-flexion position for indirect laryngoscopy. (From Bruck.[50])

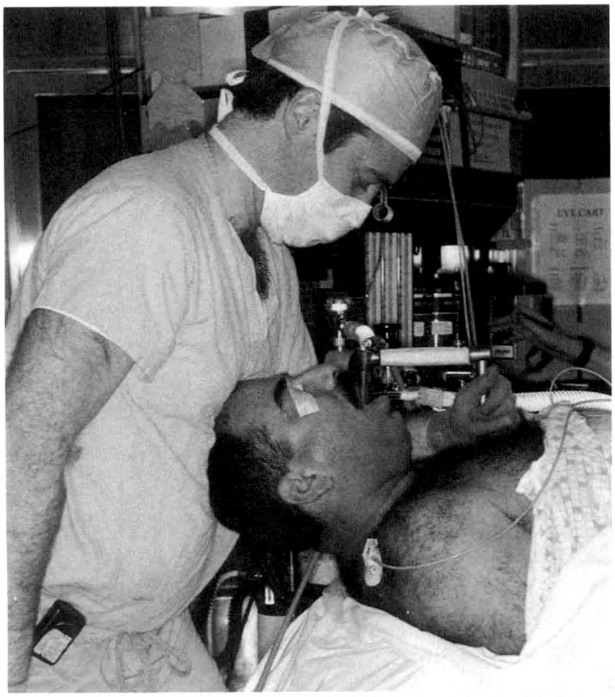

Fig 21. Patient is in flexion-flexion position to facilitate glottal exposure for difficult intubation. Clinician can support patient's head on chest or abdomen[49] if assistant is not available.

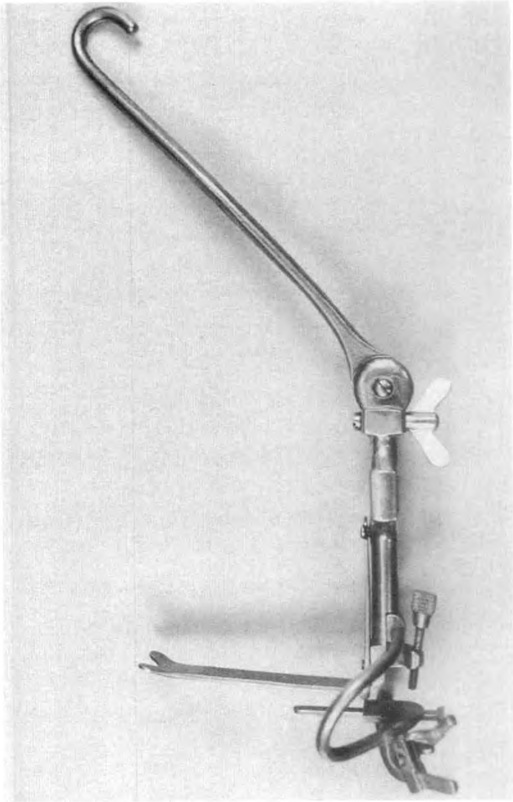

Fig 22. Early Killian suspension laryngoscope. (Courtesy of Massachusetts Eye and Ear Infirmary.)

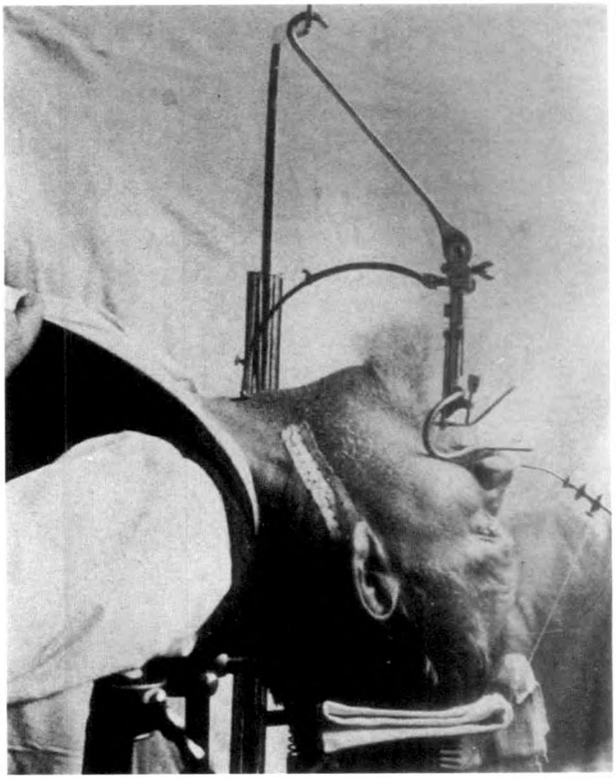

Fig 23. Brunings external counterpressure device retrofitted to Killian's suspension laryngoscope. This was necessary, because patient was not in ideal extension-extension position. (From Jackson.[12])

noted by Johnston[51] 85 years earlier, a recent study[49] demonstrated that flexion of the head and neck[49,52] most reliably achieved the most complete exposure of the anterior glottis, especially with the largest laryngoscope. These data suggest that pure flexion (Figs 20 and 21[49]) is the position of choice for difficult exposure during direct laryngoscopic endotracheal intubation (Fig 21).

The study[49] also confirmed that the interarytenoid region could be adequately exposed in pure extension position with a small laryngoscope in most patients, as is the typical requirement for intubation. Finally, the investigation explained why there was great success at the turn of the century with catheter placement by means of narrow-lumen tubular laryngoscopes for anesthetic endotracheal insufflation.[4,6] Larger endotracheal tubes with distal cuffs would be introduced later. The pure flexion position was technically unfeasible for microlaryngoscopic surgery, because the proximal lumen of the laryngoscope is directed toward the ceiling (Fig 21). Therefore, the Boyce-Jackson position was confirmed experimentally to be the ideal position for microlaryngoscopic surgery.[49,52]

Suspension Laryngoscopy, and Torsion-Fulcrum Laryngoscope Holders. Suspension laryngoscopy improved the precision of endolaryngeal surgery by allowing for bimanual tissue manipulation, which revolutionized the technique. Killian introduced his suspension laryngoscope (Figs 10, 11, 22, and 23[12]) in 1912, and the modified tongue spatula(s) soon thereafter. However, he placed the patient in pure extension (Figs 10 and 23), which was a suboptimal position for exposure of the glottis.

The author has not been able to determine why Jackson never adopted suspension laryngoscopy and accompanying bimanual surgery, and why Killian never adopted the Boyce-Jackson position to improve exposure. This is surprising, considering their academic collaborative relationship. Killian's chapter[53] describing suspension laryngoscopy in Jackson's text *Peroral Endoscopy and Laryngeal Surgery* is the only section not authored by Jackson.

Killian, Jackson, Kirstein, and Green all retained a similar philosophy: the appropriate application of force during direct laryngoscopy was to the tongue-mandible complex. They did not use the maxilla as a fulcrum for the laryngoscope blade, which would then serve as a lever to expose the anterior glottis. In contradistinction, most surgeons today utilize a torsion laryngoscope holder-stabilizer, which applies the primary force from the chest wall or a stand to the maxilla for obtaining anterior glottal exposure.

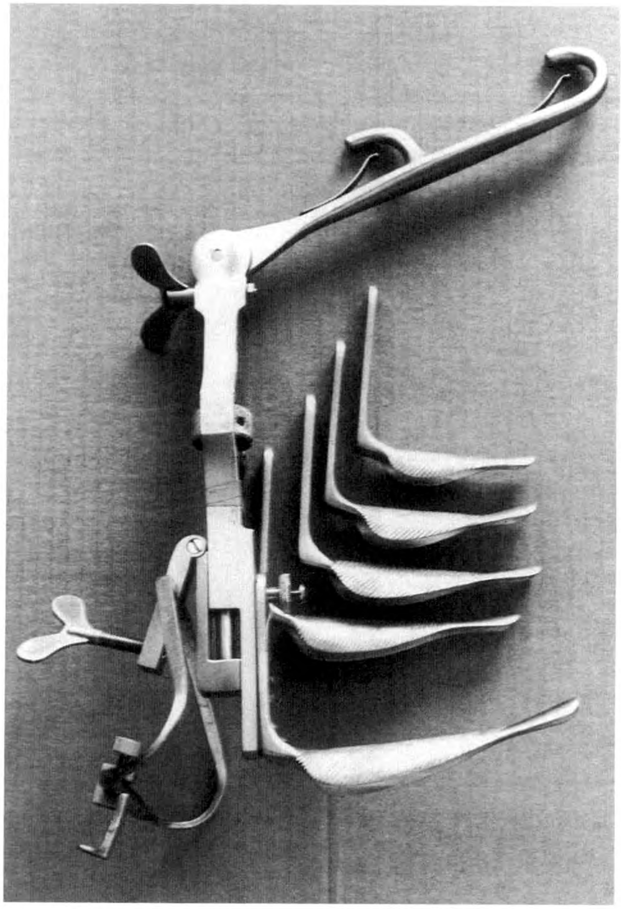

Fig 24. Lynch suspension laryngoscope system. (Collection of S. Zeitels.)

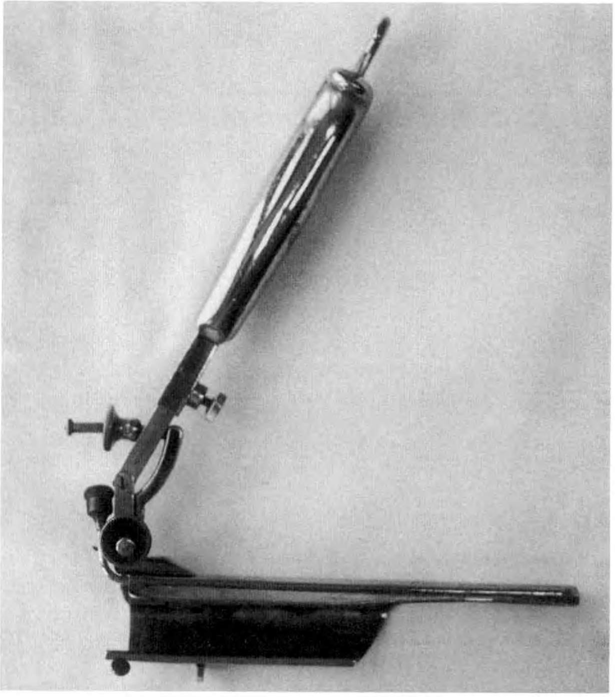

Fig 25. Mosher suspension laryngoscope. (Courtesy of Massachusetts Eye and Ear Infirmary.)

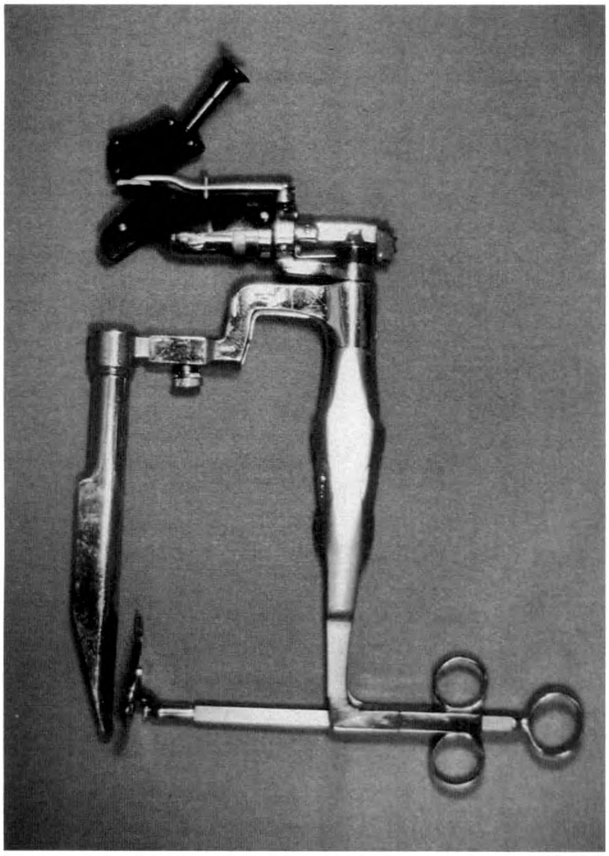

Fig 26. Brunings external counterpressure spatula laryngoscope. Magnifying telescope (not seen) or extension eyepiece for second observer could be attached. (Collection of R. Garcia-Tapia.)

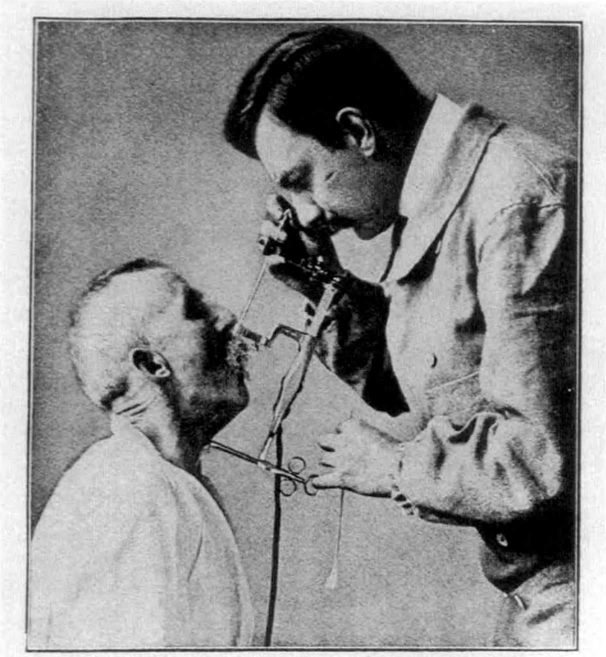

Fig 27. Brunings performing sitting direct laryngoscopy with his external counterpressure laryngoscope. (From Brunings.[56])

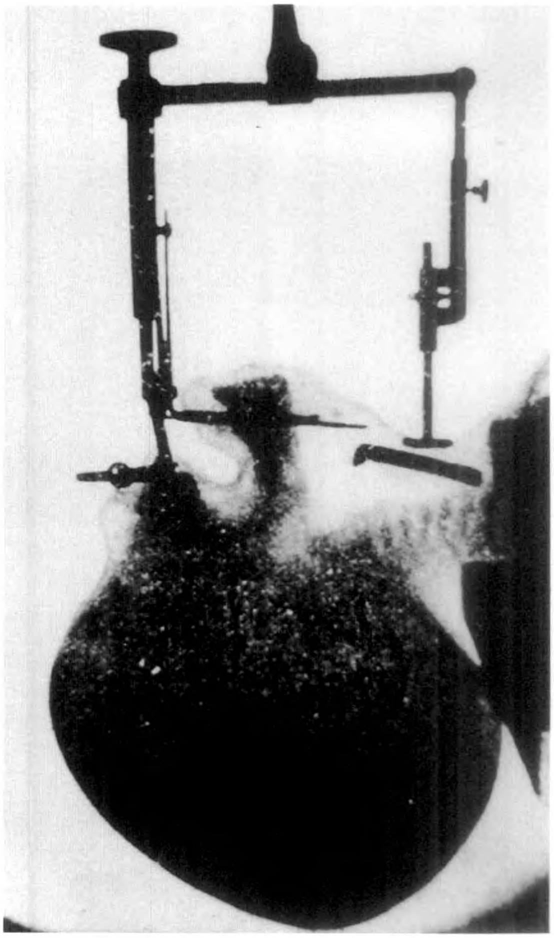

Fig 28. Radiograph demonstrating old modified Killian suspension laryngoscope, which is placed in cadaver that is in head-hanging position. Visualization of glottis is improved by Brunings external counterpressure device. Mechanical advantage of device is well seen because of O'Dwyer tube in airway. (From Zeitels and Vaughan.[42])

Suspension laryngoscopy requires that the patient be hanging from some type of gallows, as described by Killian (Fig 10),[34,37,38,53] Lynch (Fig 24),[54,55] and Mosher (Fig 25).[43] Torsion-fulcrum stabilizing devices were reported by Killian's disciples Brunings[56] and Seiffert, since they desired to perform bimanual surgery and found suspension laryngoscopy too difficult. Brunings cleverly stabilized his spatula laryngoscope by applying external counterpressure to the laryngeal cartilage framework (Figs 26, 27,[56] 28,[42] and 29), while Seiffert utilized the chest wall[57] (Fig 30). With a fulcrum laryngoscope stabilizer or holder, the movement of a spatula or tube within the laryngeal introitus to expose the anterior glottis is analogous to that of an oar, with the maxilla as the oarlock.

In the first half of the century, those who used tubular laryngoscopes operated with one hand as described by Jackson. Bimanual surgery with a suspension laryngoscope was done with spatula blades

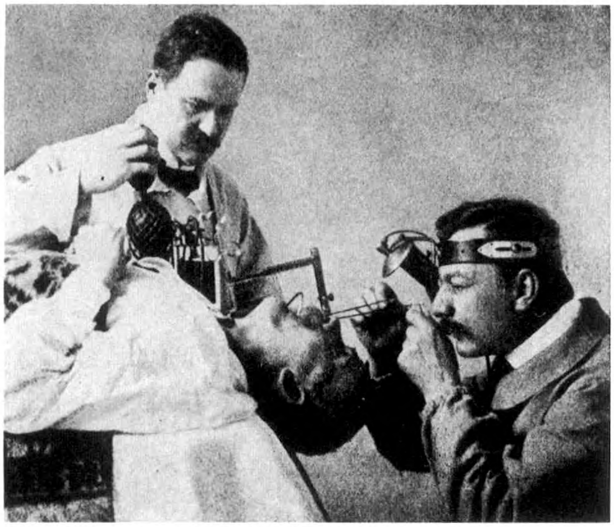

Fig 29. Brunings performing bimanual endolaryngeal surgery with his laryngoscope and headlight for illumination.

and was practiced by a minority of surgeons, many of whom were directly influenced by Killian and Lynch.[58-60] After World War II, Roberts[44,45] modified Haslinger's tubular laryngoscope (Fig 31) and added a chest-support stabilizer (Fig 15) to maintain position of the instrument for bimanual endolaryngeal surgery. Later, King[61] and Sommers[62] retrofitted stabilizing devices to Jackson-type C-shaped laryngoscopes.

Subsequent to these reports, Lewy[63] introduced a similar laryngoscope stabilizer with a gear-power advantage, which became quite popular, since most otolaryngologists continued to find suspension laryngoscopy difficult to perform prior to the use of general anesthesia. During the era in which Lewy's laryngoscope holder was introduced (1950s), general endotracheal anesthesia was not typically employed in conjunction with direct laryngoscopy. His gear-powered device was easy to use and enabled a large number of surgeons to perform bimanual surgery who had previously been unsuccessful with suspension techniques. This was very important for the development of endolaryngeal surgery in the middle part of the century. However, Lewy referred to his laryngoscope holder as a suspension device, and that incorrect terminology persists. *Webster's*[64] defines the word "suspend" as "to hang so as to be free on all sides except at the point of support; as to suspend a ball by a thread."

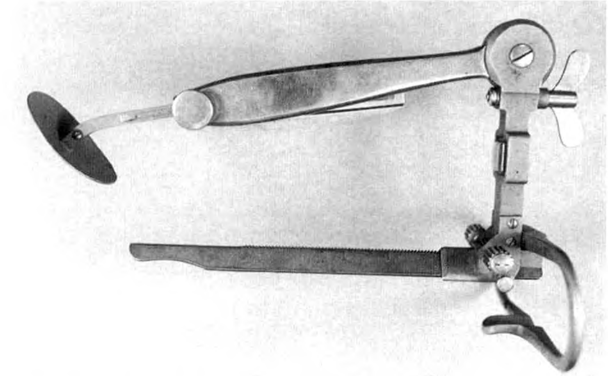

Fig 30. Seiffert's chest-support fulcrum spatula laryngoscope. Current laryngoscope holders were derived from this instrument. Spatula had inverted V conformation. (Courtesy of Massachusetts Eye and Ear Infirmary.)

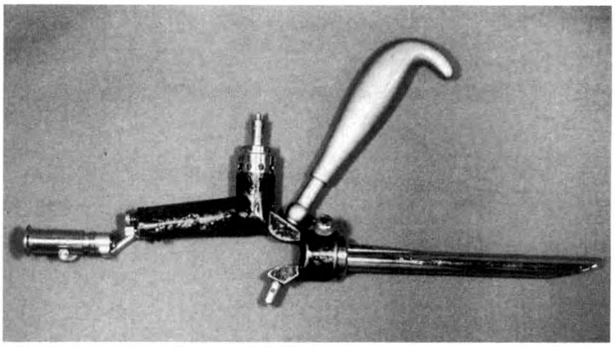

Fig 31. Haslinger tubular laryngoscope with magnifying telescope. (Collection of R. Garcia-Tapia.)

This misunderstanding of suspension laryngoscopy resulted in the obscuration of the tremendous cumulative experience and knowledge of Kirstein, Killian, and Jackson, even to the present. Laryngoscope holders became popular throughout the world in the 1950s and 1960s. The use of these devices should have been supplanted by suspension laryngoscopy in the 1960s, when general endotracheal anesthesia with paralysis was popularized with direct laryngoscopy.[65] Improvements in anesthesia brought true suspension laryngoscopy within the purview of most surgeons. Thomas,[66] as well as the Boston University group,[67] realized this and introduced true suspension systems; however, surgical habits are slow to change. The reader is encouraged to critically review the primary sources regarding laryngoscope holders and suspension gallows to develop an unbiased perspective on the development of this instrumentation.

A return to suspension laryngoscopy would be advantageous to surgeons who use laryngoscope holder-stabilizers. Current phonomicrosurgical techniques are optimized by obtaining the widest possible glottal surgical field. This is accomplished by placing the largest-diameter well-designed laryngoscope that can be inserted between the lips and the glottis and can only be achieved if the patient is suspended by the supraglottal and pharyngeal tissues in the Boyce-Jackson position.[68] This approach represents the convergence of Kirstein's, Killian's, and Jackson's techniques and is termed elevated-vector

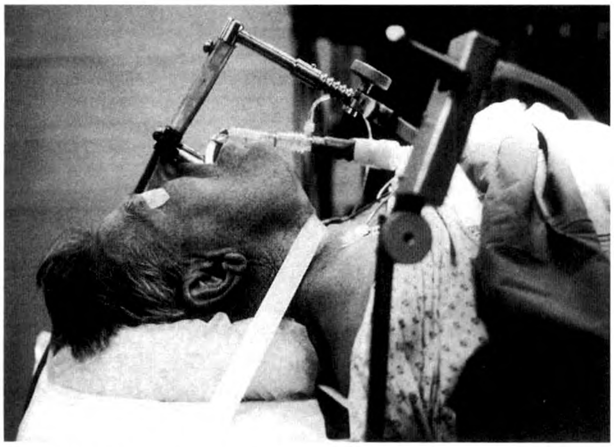

Fig 32. Patient in Boyce-Jackson position being maintained by Boston University gallows to achieve elevated-vector suspension. External counterpressure is applied with silk tape. (From Zeitels and Vaughan.[42])

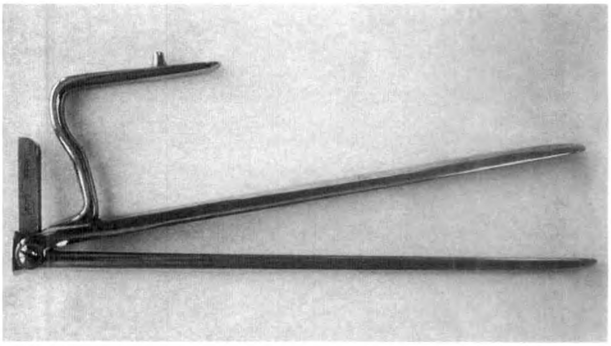

Fig 34. Killian's distending bivalved hypopharynx spatula, which attached to universal handle. (Courtesy of Massachusetts Eye and Ear Infirmary.)

suspension[14] (Fig 32[42]).

External Counterpressure, Internal Distention, and Bivalved Laryngoscopes. Czermak employed external counterpressure (Fig 16) to the cartilage framework while performing indirect laryngoscopy to improve exposure. Brunings described the technique more formally and retrofitted a number of suspension laryngoscopes (Figs 23 and 26-29) that applied significant force to the lower laryngeal cartilage framework to enhance exposure of the anterior glottis. External counterpressure has been used informally by means of manual compression throughout this century in performing endolaryngeal surgery and endotracheal intubation. Recently, the concept was formally discussed by Zeitels and Vaughan[42] to illustrate the advantages for enhancing laryngoscopic exposure. They applied silk tape stretching from the operating table across the lower laryngeal cartilage framework. Subsequently, Corbridge and Harries[69] introduced a novel laryngeal cushion to further enhance the exposure provided by external counterpressure.

Internal distention represents the distraction of pharyngeal and supraglottal tissues so that the laryngeal introitus can be visualized more completely. This idea was first applied in Babington's "glottoscope" (1829), which comprised a laryngeal mirror and an accompanying spatula (Fig 33[30]) to retract the tongue base anteriorly for enhancing endolaryngeal visualization. Anteroposterior internal distention was incorporated into Killian's turn-of-the-century bivalved distending hypopharynx speculum (Fig 34). Internal distention does not appear to have been formally described for direct laryngoscopy until Haslinger introduced the bivalved laryngoscopes[40,70] (Figs 35-37). Roberts' ingenious modification of Haslinger's tubular laryngoscope created distal internal distention by means of a hinged flange on the bottom of the laryngoscope tube (Fig 15).

Most subsequent current-day bivalved spatula laryngoscopes[71,72] also employ anteroposterior internal distention. However, the distending force gener-

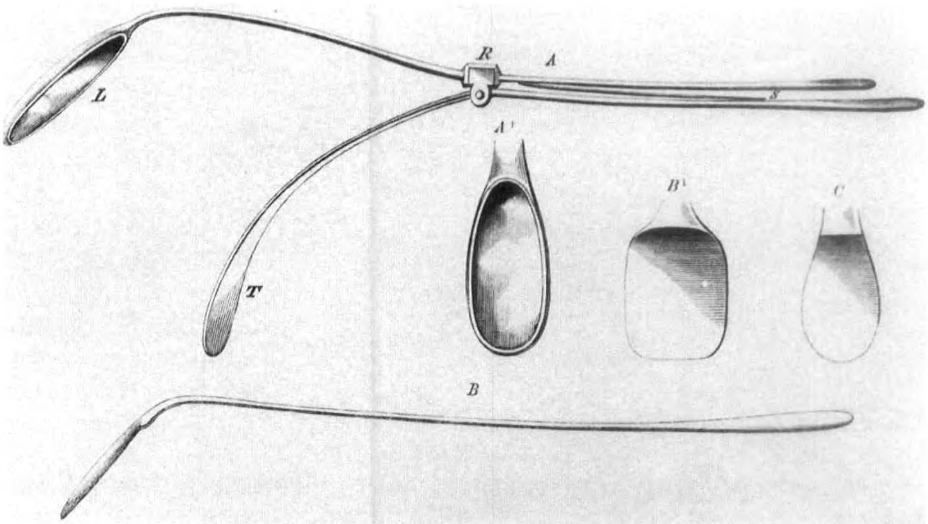

Fig 33. Babington's "glottoscope" (1829) had self-contained spatula to distract tongue base out of visual field. (From Mackenzie.[30])

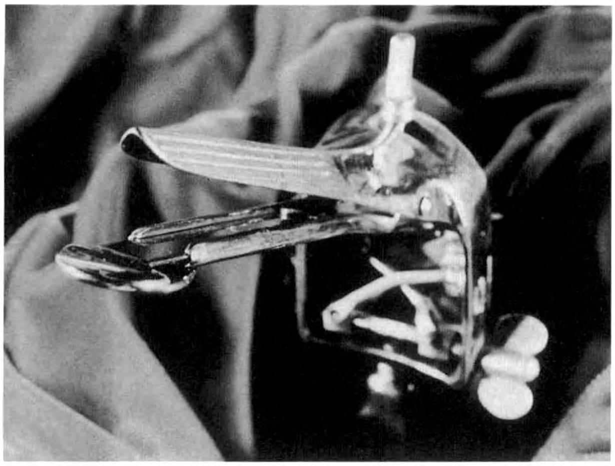

Fig 35. Haslinger's bivalved distending spatula laryngoscope (directoscope) had inverted V configuration to conform to anterior commissure. (Collection of Collin Karmody.)

ated at the proximal handle does not successfully transmit to the distal tip of the laryngoscope blade, which is engaging the laryngeal tissues. A great advantage of bivalved laryngoscopes is that hand instruments can be brought in easily between the spatula blades and into the scope lumen, which is important in using lasers that have large delivery systems that are attached to the microscope. More important, hand instruments can be angulated between the spatula blades for enhanced tissue retraction in the laryngeal surgical field.

Jackson, Tucker, and Clerf[41] described internal distention with medial-to-lateral distraction of the vestibular folds to enhance visualization of the musculomembranous vocal folds during endoscopic glottal surgery. They explained that patients were awake and frequently coughing, and that the laryngostat ensured an adequate view of the vocal folds. As mentioned earlier, the laryngostat was a teardrop-shaped tubular laryngoscope that conformed to the anterior commissure and maintained the vestibular folds laterally. Priest and Wesolowski[65] also discussed the importance of lateral distraction of the vestibular folds in a landmark manuscript that described direct laryngoscopy with general endotracheal anesthesia.

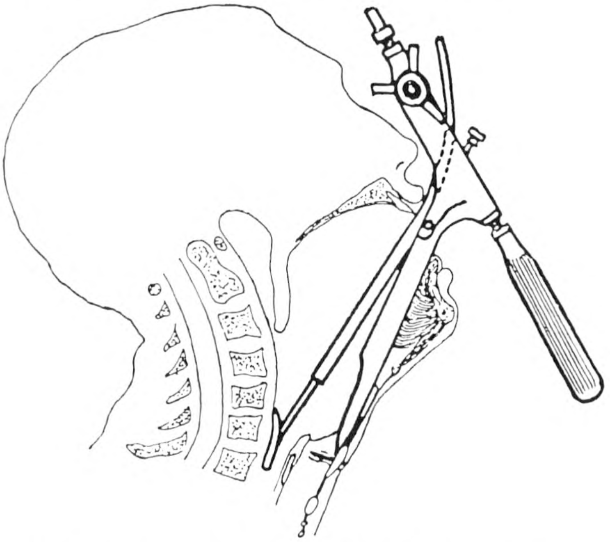

Fig 36. Schematic of Haslinger's spatula laryngoscope. (Collection of Collin Karmody.)

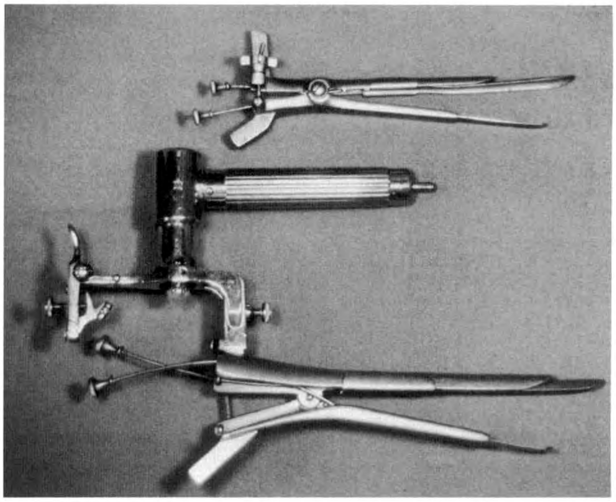

Fig 37. Another Haslinger bivalved spatula laryngoscope with telescoping blades. (Collection of R. Garcia-Tapia.)

Magnified Laryngoscopy and Carbon Dioxide Laser. A magnified view of the larynx was first reported in 1895 by Oertel[33] in his description of the mirror-guided stroboscope (Fig 38[33]). Brunings[56] also utilized a magnified ocular and was the first to employ magnification to enhance direct laryngoscopy. Haslinger also designed a tubular laryngoscope with accompanying telescopic magnification (Fig 31). Kahler's panelectroscope[43] probably had magnification capabilities as well. In the early 1950s, Albrecht[73] used a colposcope for magnified indirect vocal fold examination and for photodocumentation of keratosis. The first published report of the use of the surgical microscope during laryngoscopy was by Scalco, Shipman, and Tabb[74] in 1960; they employed the Lynch spatula suspension laryngoscope for the task. The surgical microscope was a monumental innovation for enhancing the precision of endolaryngeal surgery, because it provided high-power magnification with a 3-dimensional stereoscopic field.

Jako[75,76] (in the United States) and Kleinsasser[46,77] (in Europe) perfected surgical microlaryngoscopy. Jako[75] introduced the first set of microlaryngeal hand instruments, and Kleinsasser[46] introduced the 400-mm lens. The latter innovation increased the working distance between the microscope lens and the proximal lumen of the laryngoscope, facilitating the placement of the long-shafted otologic instruments. Both surgeons designed wide-bore examining tubes

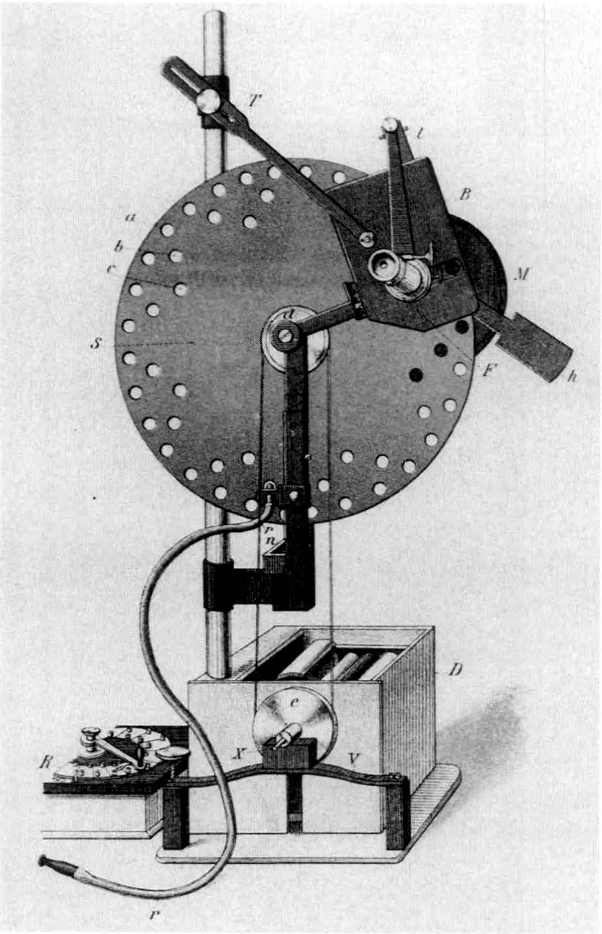

Fig 38. Oertel's laryngostroboscope (1895). (From Oertel.[33])

to accommodate the optical characteristics of the surgical microscope. Strong[78,79] and DeSanto and Carney[80] systematically discussed microlaryngeal surgery, which broadened its appeal in the United States.

Kleinsasser[46,81] designed his own hand instrumentation and established the foundations for cold-instrument microlaryngoscopic technique, which has recently enjoyed renewed enthusiasm as phonomicrosurgical procedures have increased in popularity.[14,82-90] Today, most phonomicrosurgical procedures should be performed under 25× or 40× magnification to ensure maximal preservation of the vocal folds' layered microstructure (laminae propriae and epithelium).[90-94]

Jako,[95] in cooperation with Polanyi et al,[96] Strong and Jako,[97] and Vaughan,[98] went on to introduce the carbon dioxide (CO_2) laser to surgery, by joining it to the surgical microscope. The CO_2 laser enhances cold instruments when the lesion is vascular or too large to be adequately retracted within the laryngoscope.[90] The laser is a valuable component of the laryngologist's armamentarium (as an energy source to manipulate tissue), and its role will probably expand again in coming years with further breakthroughs in laser technology. The CO_2 laser provides excellent hemostasis as well as a stable delivery system (joystick and foot pedal) for those who have difficulty maintaining dexterity in their nondominant hand under high magnification (personal communication, 1994, M. S. Strong).

Illumination. The initial illumination for direct laryngoscopy was sunlight.[1] As a result of the introduction of electricity, Kirstein[2] used a headlight (Fig 5) with his initial autoscope spatula. Subsequently, he designed an electrified handle (Fig 7) with a proximal incandescent bulb and a prism to direct the light distally.[3] Later, Jackson introduced distal illumination by means of electrified light carriers.[9] Holinger[99] explained that little changed until "Broyles first demonstrated the advantage of fiberoptic light transmission in peroral endoscopes..." during his address as the guest of honor of the American Broncho-Esophagological Association in 1962.[100] About the same time, the additional light provided by the surgical microscope enhanced the self-contained illumination of the direct laryngoscopes. There has not been a dramatic change since then.

PARADOXES IN DIRECT LARYNGOSCOPE DESIGN AND TECHNIQUE

Since Kirstein formally introduced the first direct laryngoscope, a multitude of variations on this instrument have been designed to enhance endolaryngeal surgery and endotracheal intubation. All of these rigid laryngoscopes employ a spatula(s) or a tube to provide visualization of the laryngeal field. The construction and function of more than 50 of these laryngoscopes were analyzed to make the following observations, which reflect design flaws based on current technique requirements. Categorizing the design deficiencies of each instrument is an inefficacious use of time and would likely lead to ill sentiment, since most laryngologists and anesthesiologists are content with their instrumentation. Therefore, observations are delineated without ascribing characteristics to specific laryngoscopes. Clinicians will be able to individualize the value of these observations on the basis of their personal preference and experience.

TERMINOLOGY

"Laryngoscope" is a generic term for a device that is used to visualize the larynx. In the 19th century, a laryngoscope was a mirror. The anatomy of the larynx is complex enough so that it is reasonable to stratify laryngoscopes by the specific tissues that they are designed to expose. As subglottiscopes[101] and supraglottiscopes[102] have been introduced, it seems prudent to use the term glottiscope if the instrument is fashioned to exclusively expose the vocal folds. The precedent for the use of the term glottiscope (glottoscope) was actually established by Babington[103] (Fig 33) in 1829, about 30 years before the field of laryngology developed.

LARYNGOSCOPE BLADE DESIGN

Distal Lumen. The distal lumen of most tubular laryngoscopes designed for glottal surgery is circular or oval, yet the glottal shape is most similar to a triangle. For this reason, laryngoscopes are typically situated cephalad to the vestibular folds, precluding internal distention[42] and optimal exposure of the true vocal folds. The inverted V concept for spatula laryngoscopes (Figs 11, 30, and 35) should be incorporated into tubular laryngoscopes for adequate internal distention of the supraglottal tissues. Jackson et al[41] designed the teardrop-shaped laryngostat to achieve this; however, it was a small-lumen monocular instrument conceived prior to microlaryngoscopy. Broyles also employed monocular variations of Jackson's laryngostat that conformed to the anterior commissure while distracting the vestibular folds.[65] Interestingly, a laryngostat was described for use in the first report of rigid laryngoscopy with general endotracheal anesthesia.[65] Later, Vaughan[68] elucidated the importance of this principle for effective exposure in phonomicrosurgery. Using prototype laryngoscopes that adequately exposed the anterior commissure, Desloge and Zeitels[104] dispelled some of the myths regarding surgery (for benign and malignant disease) in that region in a series of 115 patients.

Tube Contour. There is no controversy that tubular glottiscopes should taper from a wider proximal lumen to the narrower distal aperture to accommodate the optical properties of the surgical microscope. Many laryngoscopes have a wider proximal aperture than is required for use with the microscope to facilitate angulation of hand instruments. Excessive widening of the proximal lumen can inhibit distal placement of the laryngoscope examining tube,[49,65] since the widened proximal lumen cannot be inserted through the oral cavity and within the inner diameter of the mandible. This can result in 2 problems. The distal end of the scope is cephalad to the vestibular folds, so that internal distention of these structures is not achieved and exposure of the vocal folds (especially the superior surface) is not optimal. Additionally, as more of the laryngoscope tube is outside the oral cavity, the distance between the surgical microscope and the proximal laryngoscope lumen is decreased. This can actually preclude placement of hand instruments despite the 400-mm lens (40-cm working distance). The micromanipulator of the CO2 laser is attached to the microscope lens and thus also results in the loss of working distance between the microscope and the proximal lumen of the laryngoscope.

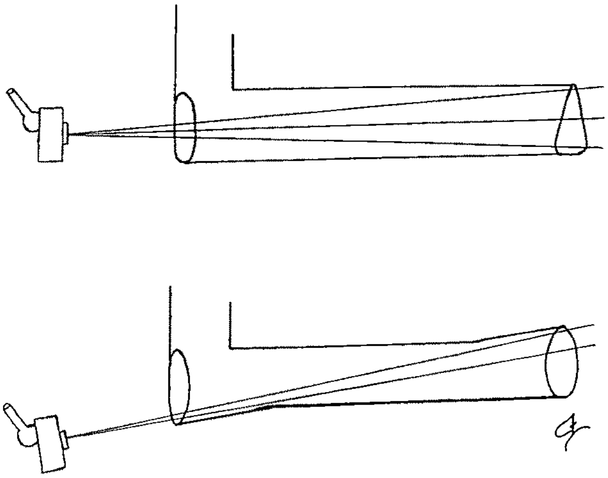

Fig 39. Diagrammatic representation of microlaryngoscopic exposure through tubular laryngoscopes. Hourglass configuration of lower one requires microscope to be poorly positioned when utilizing anterior flare. (From Zeitels.[14])

Another common design flaw of current tubular laryngoscopes is due to the perception about the ideal characteristics of an "anterior commissure" scope, which is hourglass in configuration. These instruments were excellent when they were introduced[105] in the mid-20th century, prior to the use of the surgical microscope or the CO2 laser. *At the time these laryngoscopes were conceived, they worked quite well, because endolaryngeal surgery was done with both the surgeon and the patient (adjusted by the head-holder assistant) mobile (Fig 19). The hourglass configuration is cumbersome at best during microlaryngoscopy (Fig 39[14]), because the typical immobility of both the patient and the surgeon during the procedure precludes adjustment to the ideal optical vector.*

The hourglass shape was not found in the original tubular laryngoscopes[46,47,77,106] designed for use with the surgical microscope. Neither the optical pathway of the microscope nor the CO2 laser[95,97] (introduced later) can bend around the central narrowing. Although Dedo's microscope-compatible laryngoscope was wider than previous "anterior commissure" laryngoscopes, it retained an hourglass configuration, limiting full microstereoscopic view of the distal lumen. Additionally, to utilize the anterior flare, the microscope must be malpositioned in a way that can interfere with the range of the focusing beam of the CO2 laser (Fig 39).

A microscope-compatible laryngoscope is properly contoured when a stereoscopic view through the proximal lumen encompasses the entire distal lumen.

In contradistinction, one current instrument with an hourglass shape has an internal telescope (in order to bypass the compromised viewing aperture) that reduces the critical intraluminal working area of the laryngoscope. The shafts of accompanying hand instruments are then bent to accommodate the hourglass distal flare, and the bending limits the maneuverability of those instruments within the lumen of the laryngoscope. The enigmatic engineering logic of this approach is fraught with interdependent flaws. Further, it has been suggested that the surgeon utilize this laryngoscope by operating from the telescope-generated monitor image, since there is difficulty viewing the tips of the bent hand instruments. Conceptually, this disregards magnified 3-dimensional endolaryngeal surgical technique, one of the most critical innovations of the 20th century.

Handle Design. The ideal handle should be ergonomically comfortable for manual gripping and for exertion of force as necessary. An L-shaped design as originally described by Kirstein is adequate for most intubations. Typically, the pharyngeal and supraglottal soft tissues are easily distracted to expose the interarytenoid region, and the sniffing position with the head off the table is unnecessary.[49] If the exposure is difficult, a C-shaped handle is ideally suited to apply the appropriate vector force near the distal aspect of the laryngoscope blade. Killian,[37,53] Lynch,[54,55] Thomas,[66] Grundfast et al,[67] and Andrews[107] were keenly aware of this vector-force requirement of suspension laryngoscopy. The L-shaped hinged handle probably became popular among anesthesiologists in mobile army hospitals, where the laryngoscope was folded into a pocket for portability. This requirement is less crucial for most conventional hospital settings.

Adjustability and Modular Design. Despite the fact that the first direct laryngoscope[2] was modular, with a universal handle and detachable blades, most current tubular laryngoscopes are single units with fixed handles. There is relatively little variation in laryngoscope blades in any specific model, despite the wide variation in anatomy based on age, gender, and disorders of the head and neck. Anatomic variation was recognized by those who designed suspension laryngoscope systems (Killian, Lynch, Seiffert), since a plurality of spatula blades were attachable to a universal handle. The lack of a modular universal handle, which is designed to accompany a spectrum of detachable tubes, has limited surgeons' choice, created a more cumbersome operating setup, and increased expense.

MATERIALS AND METHODS

The design features for this new laryngoscope were conceived over a decade ago. After careful discussions with G. Jako, C. W. Vaughan, and M. S. Strong about their experiences with conventional paradigms for instrument design and production, the author decided to wait until resources were available to pursue the new laryngoscope independent of existing corporate sponsorship.

The laryngoscope was computer-modeled in the solid modeling program Pro/Engineer (Parametric Technologies Corporation, Waltham, Mass). Various sections were generated, and a smooth surface was interpolated between them. The finite element analysis program Pro/Mechanica (Parametric Technologies Corporation) was used to determine the structural integrity of the laryngoscope. This program allowed for the simulation of actual working loads and conditions to be applied to the computer model and provided the resulting stresses. The geometry of the laryngoscope was then refined and reanalyzed to provide maximum strength while maintaining the desired form and fit. Metallurgists were consulted for selecting the ideal composition of the components.

RESULTS

The UM glottiscope (Figs 40-45) evolved from the 1) selection of ideal prior design features, 2) development of novel innovations, 3) assessment of prior surgeons' experiences, 4) evaluation of present and future phonomicrosurgical procedures, and 5) utilization of computer-generated engineering programs.

DISCUSSION

The UM glottiscope was conceived from a cen-

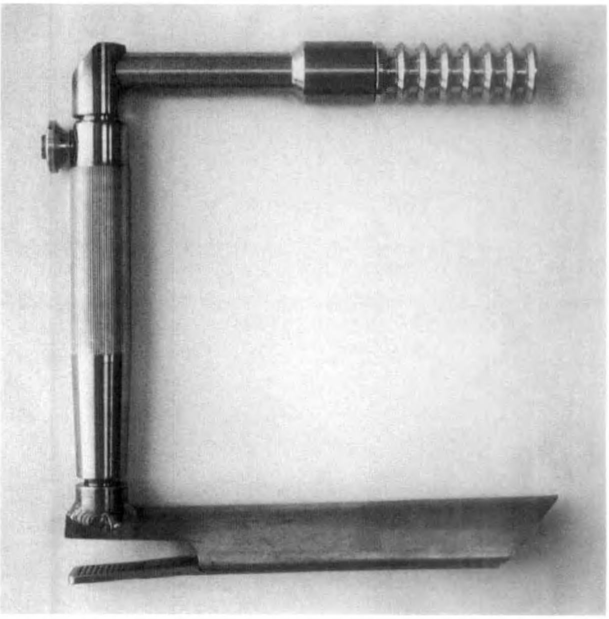

Fig 40. Universal modular glottiscope. (Endocraft® LLC, Boston, Mass; US patent 5,893,830.)

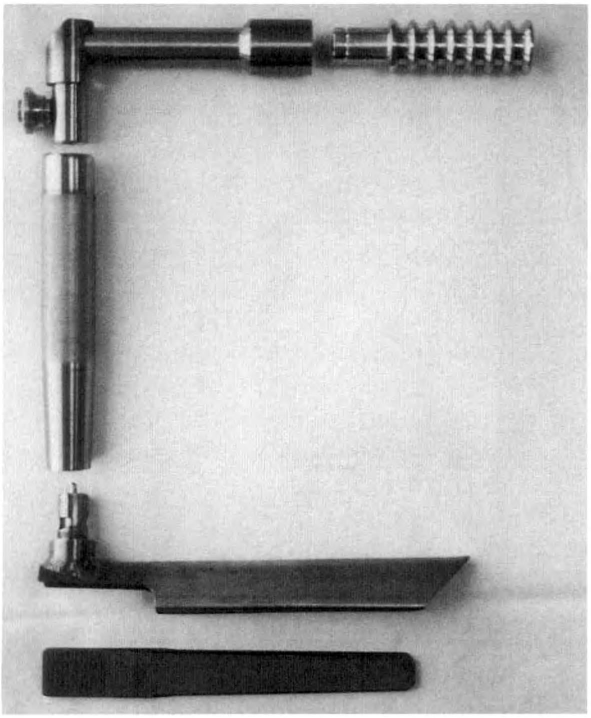

Fig 41. Modularity of universal modular glottiscope is well seen in this prototype.

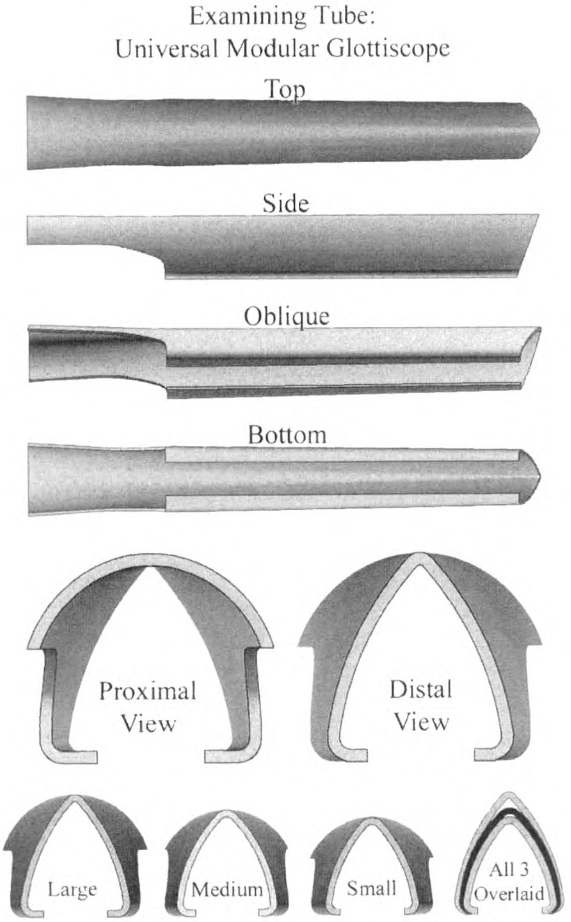

Fig 42. Diagram of examining tubes from variety of perspectives.

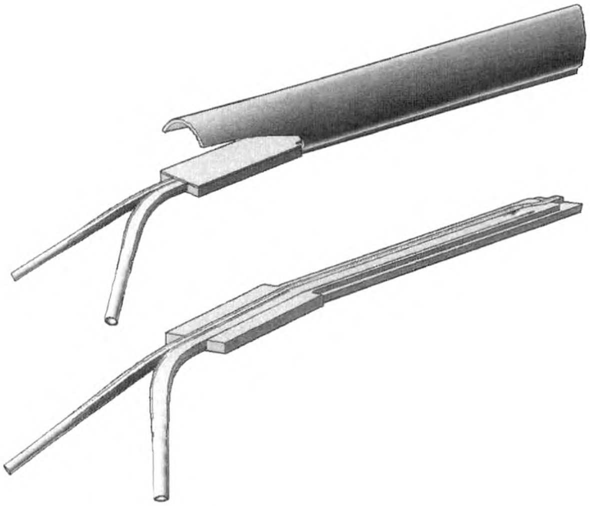

Fig 43. Diagram of baseplate separated from examining tube, displaying light carrier and suction–jet ventilation ports within its wall.

tury of direct laryngoscope designs and was intended to incorporate the most valuable prior innovations into a uniquely amalgamated instrument. The goal of this glottiscope system is to provide the clinician with a versatile laryngoscope that can optimally expose the vocal folds for diagnosis and instrumental manipulation, regardless of the diversity of human anatomic factors: age, gender, and disorders of the head and neck. As is typically the case when there are a large number of instruments available to serve a similar purpose, no existing glottiscopes have distinguished themselves as being superior in quality and design or gained universal acceptance.

DISTAL LUMEN OF LARYNGOSCOPE TUBE

The distal lumen of the UM glottiscope is an isosceles triangle shape with arcuate sides (Figs 42 and 45) that create a lancet arch conformation. Unlike

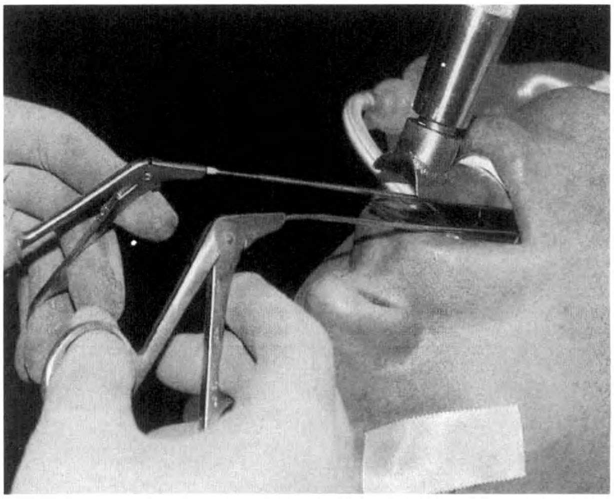

Fig 44. Hand instruments are angulated by positioning them through bilateral proximal slots.

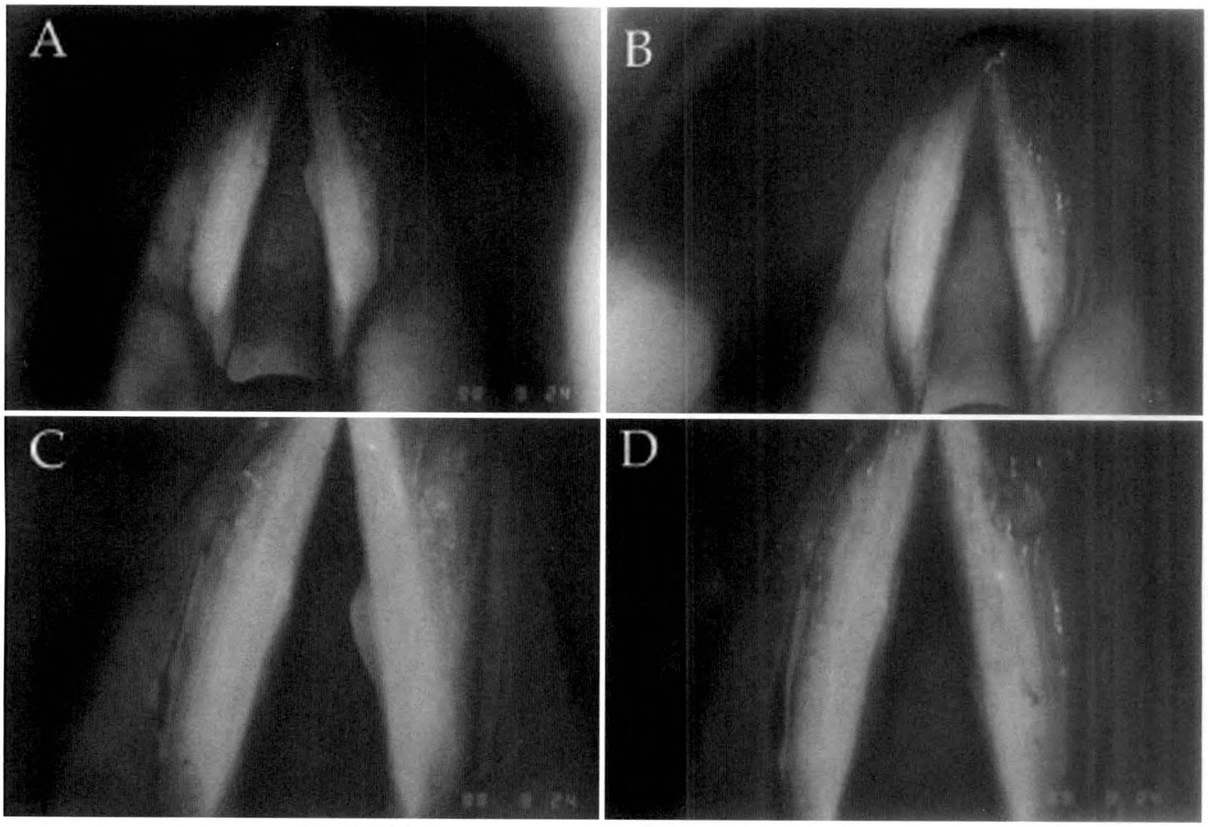

Fig 45. Right-sided polyp and left-sided nodule are viewed through arch-shaped tube of universal modular glottiscope. Scope has been positioned to display more of right vocal fold, which has larger lesion. Note that superior surface of anterior commissure is well seen, as well as significant amount of superior surface of vocal folds. Subepithelial resection of lesions was performed. A) Preexcision. B) Postexcision. C) Preexcision, higher magnification. D) Postexcision, higher magnification.

Jackson's laryngostat,[41] which was designed prior to the use of endotracheal anesthesia with endolaryngeal vocal fold surgery, the UM glottiscope has a flat planar base. Jackson's laryngostat was appropriately curved at the base to conform to the interarytenoid region. Holinger's anterior commissure scope[105] had a longer distal (teardrop-shaped) aperture than was found in the laryngostat (because of an increased distal flare). This was an important improvement at the time, because this shape expanded supraglottal internal distention and, in turn, vocal fold exposure.

However, these experienced laryngologists did not perform laryngoscopy with an endotracheal tube in place. The planar base of the UM glottiscope rests on the endotracheal tube, maintaining the tube between the arytenoids for optimal exposure of the musculomembranous vocal folds. The arcuate-sided distal-triangular lumen of the UM glottiscope is distinct from that of most microscope-compatible laryngoscopes, which are circular or oval. This shape is ideal for internal distention of supraglottal tissues, since the triangular tube with arcuate sides can be intercalated (with reasonable force) between the endotracheal tube and the infrapetiole region of the supraglottis.[42,52] Jet ventilation is not typically used by the author for phonomicrosurgery on the musculomembranous vocal folds, because internal distention is limited without an endotracheal tube, and because the surgical field is less stable under 25× and 40× magnification with jetting.

The ideal distal lumen of a glottiscope can be loosely envisioned in the following fashion. In the era prior to general anesthesia, the surgical exposure of the glottal introitus was roughly in the shape of an inverted ice cream cone, similar to that with Holinger's laryngoscope. Today the endotracheal tube is in the location in which the "ice cream" would be situated, so that the UM glottiscope simulates the "cone," which would have a flat planar base.

TUBE CONTOUR

The UM glottiscope tapers from the proximal lumen to the distal one to accommodate the stereoscopic optical properties of the surgical microscope. The narrow arch-shaped contour of the top of the examining tube facilitates insertion through the oral cavity[105,108] and pharynx. Unlike virtually all other microscope-compatible tubular laryngoscopes, which further widen the proximal aperture to facilitate angulation of hand instruments, the UM glottiscope has bilateral proximal slots (Figs 40 and 42). Creating bilateral slots dramatically increases the degree of freedom for positioning hand instrumentation and facilitates the insertion of hand instruments into the laryngoscope lumen. Removing the lateral walls of the tube allows the UM glottiscope to uniquely function as a bivalved laryngoscope proximally and as a tube distally.

As stated earlier, excessive widening of the proximal lumen can inhibit distal positioning of the examining tube adjacent to the superior surface of the vocal folds.[41,65] The widened proximal lumen cannot be inserted through the oral cavity and oropharynx, within the inner diameter of the mandible.[105] When more of the examining tube lies outside the oral cavity, placement of hand instrumentation is impeded, because the working distance (exacerbated by the micromanipulator of a laser) is reduced between the surgical microscope and the laryngoscope. The surgeon may then face the difficulties encountered in the early days of microlaryngoscopy,[46,47,74] when the 400-mm lens was not available.

The UM glottiscope is not hourglass in configuration, since neither the visual vector from the microscope nor the CO2 laser could bend around a narrowing. When using the UM glottiscope, the surgeon need only minimally readjust the microscope to optimize visualization of the glottal surgical field (Figs 39 and 45). Also, the aiming beam of the laser remains centered. The hourglass shape was conceived when patients were examined without general anesthesia and the point of constriction was noted to be at the posterior floor of the mouth, at the junction of the oral cavity and oropharynx.[105] With general endotracheal anesthesia and neuromuscular paralysis, a much larger tube can be placed. Unlike most microscope-compatible laryngoscopes, the superior aspect of the UM glottiscope is arch-shaped to simulate the narrow central tube conformation of Holinger's anterior commissure laryngoscope.

TUBE CONSTRUCTION

The flat planar baseplate of the UM glottiscope is detachable (Figs 40-42) and slides into the upper arch-shaped spatula. The baseplate was initially knurled proximally (Fig 41) to facilitate manually separating it from the arch-shaped spatula and to enhance the stability of detachable light carriers and suction tubes. Currently, suction and fiberoptic lighting channels (Fig 43) are contained within the baseplate to preserve the entire intraluminal working area of the examining tube and to minimize the outer diameter of the examining tube. Additionally, the planar baseplate is bent slightly to resist mild compression forces from the maxilla, especially if a fulcrum laryngoscope holder is used to stabilize the glottiscope.

The detachable baseplate is a primary component of the bilateral slot design (Figs 42-44). When the baseplate is in place, the distal lumen of the UM glottiscope has the strength of a tubular glottiscope for effective internal distention. Distending bivalved spatulas do not have the structural integrity to maintain the distention forces that are created proximally and transmitted to the distal end of the spatula blades at the glottal aperture. The inadequate distal internal distention of bivalved spatulas is exacerbated if significant external counterpressure is applied to the lower laryngeal framework.[42] Another drawback of bivalved spatulas is that they do not prevent oral and pharyngeal tissues from insinuating themselves between the blades and obscuring visualization of the glottal surgical field.

For ease in difficult intubations as well as for maintenance and cleaning of the instrument, the baseplate of the tube can be separated even while in the patient. The concept of the separation capability of the examining tube was first introduced by Killian and Jackson[9] at the turn of the century to facilitate the placement of a rigid bronchoscope. The UM glottiscope tube is similarly designed for placement of bronchoscopes, as well as for difficult intubations, especially those made difficult by obstructing carcinomas. Arch-shaped spatula blades with a self-contained distal light-carrier will also be available for routine orotracheal intubations; the handle will contain a power source and will retain the versatile L or C shape.

HANDLE DESIGN

Despite the associated expense in raw material and machining, the UM glottiscope handle is hollow and primarily composed of titanium rather than stainless steel because of titanium's light weight, which is desirable for a laryngoscope. It has long been observed that a lighter laryngoscope improves the surgeon's manual dexterity and instrument-mediated tissue proprioception.[106]

The handle is composed of 3 elements: vertical limb, horizontal limb, and extension piece (Figs 40 and 41). These elements combine ergonomic principles of hand stability and comfort because of the potential need for the use of significant force. The vertical limb of the handle has fine knurling that facilitates stability of the gripping force by increasing the friction coefficient. At the upper aspect of the vertical handle, there is a spring lock mechanism for attachment of the horizontal portion of the UM glottiscope handle or European chest support systems.[46] The spring lock is curved so that it conforms to the inner aspect of the distal phalanges of the fingers.

The horizontal component of the handle fits easily into the vertical limb. It is excavated proximally to accommodate the curve of the index finger, thus distributing the force of lifting over a broader area during elevation of the head and neck or distraction of the pharyngeal tissues. For comfort in gripping the laryngoscope, the proximal aspect of the horizontal component has been cut at an angle to support the distal phalanx of the thumb. The shaft of the horizontal component has been designed to be compatible with standard clamp-on fulcrum laryngoscope holders.[63] At the distal end of the horizontal component, an optional handle extension can be attached for use with true suspension gallows.[67]

The proximal portion of the extension piece fits easily into the horizontal handle and is maintained in place by a novel spring lock mechanism. The body of the extension handle is composed of a series of circular ridges to act as a support for the arm of the suspension gallows. The plurality of ridges allows for a variety of linear positions for placement of the suspension arm. This facilitates precise exertion of the appropriate vector of force for different-length laryngoscope tubes.

ADJUSTABILITY AND MODULAR DESIGN

The universal modular glottiscope was designed as a series of attachable and detachable components for a variety of reasons. This arrangement facilitates precise selection of which components are necessary to purchase and which are essential for any individual procedure. This model streamlines surgical efficiency.

Specifically, there are a plurality of tubes that accompany one universal handle. The range of sizes and variations in arch conformation of the examining tubes facilitate precise accommodation of the glottiscope to the spectrum of human sizes and shapes, irrespective of gender, age, or disease. Therefore, clinicians have the ability to select which tube(s) are most likely suitable and valuable to their practice. This is cost-effective as well as more orderly in the operating suite. The detachable tubes attach to the vertical handle by means of a unique spring-loaded bayonet joining system that facilitates ease of use, as well as strength and stability.

The universality of the components vis-à-vis conventional equipment allows for selective use of portions of this system joined to other laryngoscopic instrumentation (eg, using the current handle with European bivalved distending laryngoscopes). The modularity also facilitates the use of the UM glottiscope with European chest support systems of laryngoscope stabilization. Finally, the modularity will minimize replacement costs if components become lost or broken and when future innovations are developed.

ILLUMINATION AND SUCTION

Fiberoptic light carriers and suction tubes were initially designed as easily attachable and detachable clip-on devices that could be placed or removed even when the laryngoscope was positioned in the patient. These components were designed to be situated on the planar base and mostly out of the visual field, since the planar base is slightly angulated. In turn, instrumentation of the vocal folds is not affected by these components. If desired, the light carrier could be easily removed once the patient is positioned, since the microscope light is usually sufficient for endolaryngeal surgery. Suction tubes are unnecessary if cold instruments are used and can be added if the surgeon resorts to a laser procedure. Currently, the light and suction are incorporated into the planar baseplate (Fig 43), and this setup maximizes the geometric efficiency of the examining tubes. Standard light transmission cables can be used for attachment of the light carriers.

CONCLUSIONS

1. Phonomicrosurgery of the musculomembranous vocal folds is optimized by obtaining the widest possible glottal visual field, which is done by inserting the largest tubular glottiscope that can be placed between the lips and the glottis.

2. The UM glottiscope was designed to optimize phonomicrosurgery by amalgamating a number of features that evolved from a century of progress of laryngoscopes.

3. Elevated vector suspension allows for placement of a large-diameter glottiscope between the lips and the glottis. This is achieved by applying the force vector to the supraglottal tissues and tongue-mandibular complex with the patient in the Boyce-Jackson position (extension at the atlanto-occipital joint and flexion of the neck in relation to the chest).

4. The distal aperture of the UM glottiscope examining tube has a mostly triangular shape to precisely accommodate to the conformation of the glottis.

5. The magnitude of the proximal widening of the UM glottiscope tube is limited to the optical requirements of the surgical microscope.

6. The microscope-compatible UM glottiscope contour is not hourglass in shape, since this shape is ill-suited to the optical requirements of the surgical

microscope and the delivery of CO2 laser energy.

7. The examining tube of the UM glottiscope has lateral slots proximally to facilitate the insertion of hand instruments and to maximize their range of motion, thereby simulating a bivalved scope.

8. A variety of examining tubes are available to accommodate the spectrum of human anatomy and disorders.

9. The flat planar baseplate of the examining tube enhances exposure for phonomicrosurgery by facilitating the intercalation of the glottiscope examining tube between the endotracheal tube and the infra-petiole region of the supraglottis. Therefore, jet ventilation is not typically used.

10. The planar baseplate is constructed so that the light carrier and the air portal (for suction or jet ventilation) are contained within it.

11. The baseplate can be removed to facilitate the difficult intubation or the placement of bronchoscopes.

12. The light universal handle (composed primarily of titanium) with modular components can be joined to a plurality of examining tubes and spatula blades, as well as other existing laryngoscopes.

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Laser surgery, which is one type of surgical treatment for allergic and hypertrophic rhinitis, was investigated basically and clinically. The basic investigation showed morphological changes in the nasal mucosa before and after laser surgery. Before laser surgery, hyperplasia of the mucous epithelium, thickening of the basement membrane, edema of the lamina propria mucosa, eosinophilic infiltration, and enlargement of the nasal glands were noted. After laser surgery, the nasal mucosa was covered with 1) epithelium that was squamatized or cuboidal and/or 2) columnar epithelium that was stratified. Granulation-like tissue or cicatricial tissue was found in the lamina propria mucosa. Clinically, we performed laser surgery in 204 cases. Regarding the short-term results, laser surgery was effective in 87%. In the long term, the short-term results persisted in 81% of cases treated for sneezing, 78% for nasal discharge, and 76% for nasal obstruction. From these results, we concluded that laser surgery was a useful surgical treatment for allergic and hypertrophic rhinitis.

KEY WORDS — allergic rhinitis, hypertrophic rhinitis, laser surgery, morphological changes.

INTRODUCTION

Nasal allergy with paroxysmal and recurrent sneezing, watery discharge, and nasal obstruction has increased to the extent that it is now one of the most frequent diseases treated in our outpatient otolaryngology clinics. While medical treatment with a variety of newly developed orally administered drugs and nasal drops yields excellent results in some cases, such treatment must frequently be continued for a long time, placing burdens on patients in terms of time and cost. Moreover, some refractory cases do not respond to medical treatment, and surgical treatment may be required in cases with serious and irreversible edematous changes of the nasal mucosa.

Surgical treatment can be roughly divided into treatment of the autonomic nerve, which innervates the nasal mucosa, ie, vidian neurectomy, and surgical treatment of the mucosa of the inferior turbinate. The latter includes excision of the mucosa of the inferior turbinate, electrocoagulation, cryosurgery, chemical cautery, and laser surgery. Laser surgery for nasal diseases including nasal allergy has gradually increased since the first report on argon laser surgery for 3 cases of vasomotor rhinitis by Lenz[1] in 1977. The authors have performed laser surgery since 1986, in more than 200 cases of nasal allergy, and have obtained effective clinical results. However, at present, various institutions perform different types of laser surgery, and most of the ways in which these methods have their effect on nasal allergy are unknown.

We compared morphological findings of the nasal mucosa observed before and after laser surgery by light microscopy and by scanning electron microscopy, and elucidated the process of laser surgery by measuring the grade of nasal resistance and oxygen partial pressure in the lamina propria mucosa. In addition, we clinically investigated the usefulness of laser surgery treatment for nasal allergy through detailed analysis of short- and long-term results.

SUBJECTS

The subjects consisted of 204 patients with refractory, year-round obstructive nasal allergy treated at our department from June 1986 through November 1995, who had shown no symptomatic response to conservative treatment. However, cases in which the main cause of nasal obstruction was presumed to be severe deviation of the nasal septum or nasal polyps were excluded. As shown in Fig 1, the subjects con-

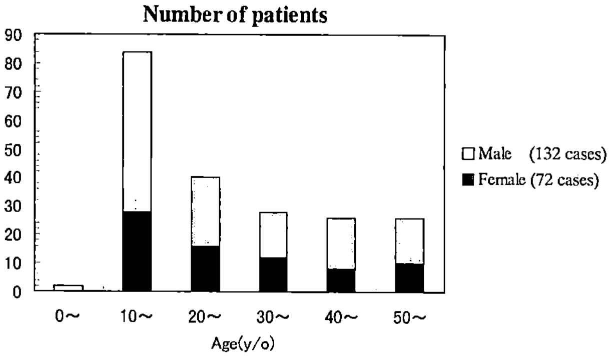

Fig 1. Composition of subjects by sex and age. Age ranged widely, from 8 to 64 years old. Most subjects were men under 30 years old (125 cases, 61.3%).

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TABLE 1. GRADING OF ALLERGIC TEST RESULTS

Tests	*3+*	*2+*	*1+*	*0*
Provocation	3 symptoms,* more than 6 sneezes	3 symptoms	2 symptoms	1 or no symptoms
Nasal eosinophilia	Clustered	Between 1+ and 3+	Scattered	None

*Sneezing, nasal discharge, and nasal blockage.

sisted of 132 males and 72 females, with ages ranging widely, from 8 to 64 years old. The majority (125 or 61.3%) were male, 10 to 29 years old, and 44 were children under 15 years old (21.6%).

A diagnosis of allergy was made in patients who showed positive results for at least 2 of 3 items consisting of the specific IgE antibody test (radioallergosorbent test; RAST), the nasal mucosa provocation test, and the nasal discharge neutrophil test, in addition to anamnesis and rhinoscopic findings. In the specific IgE antibody test, a RAST score of 2 or more for house dust was defined as positive, and the results of the provocation test for nasal mucosa and neutrophils in nasal discharge were judged according to Okuda's[2] classification (Tables 1-3). In addition, the severity of symptoms, eg, sneezing, nasal discharge, and nasal obstruction, and the severity of nasal allergy were rated according to Okuda's classification.

METHOD

Laser Surgery. Laser surgery was performed under local anesthesia in a special outpatient clinic. After intranasal superficial anesthesia with a gauze impregnated with 4% lidocaine hydrochloride diluted with 5,000-fold epinephrine, 0.5% lidocaine hydrochloride was injected. A carbon dioxide (CO_2; Ambulase model XAM-20, Xanar Co, Ltd) laser was used for 97 cases from June 1986 through May 1990, and a potassium titanyl phosphate (KTP/532) laser (Laserscope Co, Ltd) was used for 107 cases in the period from June 1990 through November 1995.

For CO_2 laser surgery, straight and reflected irradiation was performed via a hollow pipe handpiece made of aluminum, 3 mm in outer diameter. The volume of the inferior turbinate was decreased by vaporizing the anterior portion of the inferior turbinate by the straight irradiation mode, then the medial face of the inferior turbinate was vaporized toward the posterior portion as widely as possible by the reflected irradiation mode (Fig 2). The power output was 15 W (output at the tip, 9 W), continuous-wave, and had an irradiation time for 1 side of 10 to 15 minutes.

The KTP/532 laser surgery was performed to decrease the volume of the inferior turbinate by excising the area of the inferior turbinate from anterior to posterior with a handpiece for nasal surgery (Laserscope). The laser beam was transmitted via a fiberoptic quartz fiber, 0.6 mm in outer diameter, in contact with the mucosa (Fig 3). The continuous wave power output at the tip was 7 to 10 W, and the irradiation time for 1 side was about 10 minutes.

Patients were in a sitting position, and saline-immersed gauze was used to protect the area of the epipharynx and goggles were used to protect the eyes. The procedure was completed in approximately 30 minutes, and the patients went home without intranasal tampons or postoperative hemorrhage. Combined therapy such as nasal drops was not required.

Observation of Nasal Mucosa. The swelling and color of the mucosa of the inferior turbinate and the volume of nasal discharge were compared before and after treatment. Postoperative observation was made when wound healing of the nasal mucosa was anticipated to be complete, namely, 4 to 6 weeks after CO_2 laser surgery and 8 to 10 weeks after KTP/532 laser surgery.

Preoperatively and postoperatively excised nasal mucosa specimens were observed by light and scanning electron microscopy in 26 cases treated by KTP/532 laser and in 5 in which reoperation with the KTP/532 laser was performed, as well as those specimens collected with cutting forceps from patients who had given consent to evaluation of short-term (n = 21) and long-term (n = 3) results as described below.

For light microscopy, nasal mucosa specimens

TABLE 2. EVALUATION OF SEVERITY OF NASAL SYMPTOMS

	Severe	*Moderate*	*Mild*	*None*
Sneezing (average number of attacks per day)	10 times or more	Less than 10 times	Less than 5 times	0
Nasal discharge (average number of nose blowings per day)	10 times or more	Less than 10 times	Less than 5 times	0
Nasal blockage	Predominant mouth breathing	Occasional mouth breathing	No mouth breathing or sensation of blockage	0

TABLE 3. SEVERITY OF SYMPTOMS

Nasal Blockage	*Sneezing and/or Nose Blowing*		
	1-5	*6-10*	*11 or More*
Mild	Mild	Moderate	Severe
Moderate	Moderate	Moderate	Severe
Severe	Severe	Severe	Severe

were fixed in 10% formalin, embedded in paraffin, sectioned at a thickness of 3 μm, stained with hematoxylin-eosin, and observed for histopathologic changes of the epithelium and the lamina propria of the nasal mucosa.

Specimens for scanning electron microscopy were prepared by double-fixing in 2.5% glutaraldehyde-phosphate buffer and 1% osmate buffer, dehydrated with graded ethanol, replaced in isoamyl acetate solution, dried to the critical point with liquid CO_2 gas, and coated with gold by ion sputtering. A scanning electron microscope (JSM-5200, Nihon Denshi) was used, and changes on the surface microstructure of the nasal mucosa were observed.

Nasal Resistance Test. To objectively evaluate nasal ventilation, nasal resistance was measured by the anterior method with a mask and a rhinomanometer (SR-11, Rion Co, Ltd; n = 45). Measurement was made after eliminating watery discharge in the nasal cavity by aspiration. Defining the measurement standard for nasal resistance as p = 100 Pa, the objective rate of improvement of nasal obstruction was evaluated by comparing total nasal resistance on inspiration before operation and at the time the short-term results were evaluated, 4 to 10 weeks after surgery.

Measurement of Oxygen Partial Pressure in Lamina Propria Mucosa. In 16 of the 204 cases, oxygen partial pressure in the lamina propria mucosa was measured before surgery and at evaluation of the short-term results (4 to 10 weeks after surgery).

By means of a continuous measuring apparatus for oxygen partial pressure in tissue (PO_2-100DW, Intermedical Co, Ltd), measurements were made by inserting a needle electrode to a depth of about 1 to 2 mm at the anterior portion of the inferior turbinate of the patient, who was in a recumbent position under no anesthesia, and waiting for about 10 minutes until the apparatus stabilized. Measurement of tissue PO_2 utilized an electrochemical phenomenon and conformed to the oxygen (O_2) electrode method to produce an O_2 diffusion current in the tissue from an oxidation-reduction reaction, ie, $O_2 + 2H_2O + 4e^- - 4OH^-$; we measured this current and calculated PO_2. The PO_2 in the nasal mucosa of normal volunteers (n = 12) was used as the control.

Evaluation of Surgical Results. Short-term results were evaluated concurrently with macroscopic observation of postoperative nasal mucosa (4 to 6 weeks after CO_2 laser surgery and 8 to 10 weeks after KTP/532 laser surgery; n = 204). The 5-grade, postoperative improvement rating was based on changes in symptoms recorded in nasal allergy diaries by the patients: disappeared (symptoms disappeared); remarkably improved (improved by 2 grades); improved (improved 1 grade); unchanged; and worsened. Moreover, the overall rate of improvement following laser surgery was evaluated on the basis of initial rhinoscopic findings, fiberscopic findings, the improvement of nasal allergy, and the severity of nasal allergy. The 5-grade classification consisted of "disappeared," "remarkably improved," "improved," "unchanged," and "worsened." Surgery of the "disappeared," "remarkably improved," and "improved" cases was defined as effective.

To measure long-term results, a questionnaire was given to 96 patients with nasal allergy who had undergone surgery more than 2 years before, between June 1986 and March 1991, and who had short-term results (postoperatively 4 to 10 weeks) showing the surgery to have been effective. This questionnaire com-

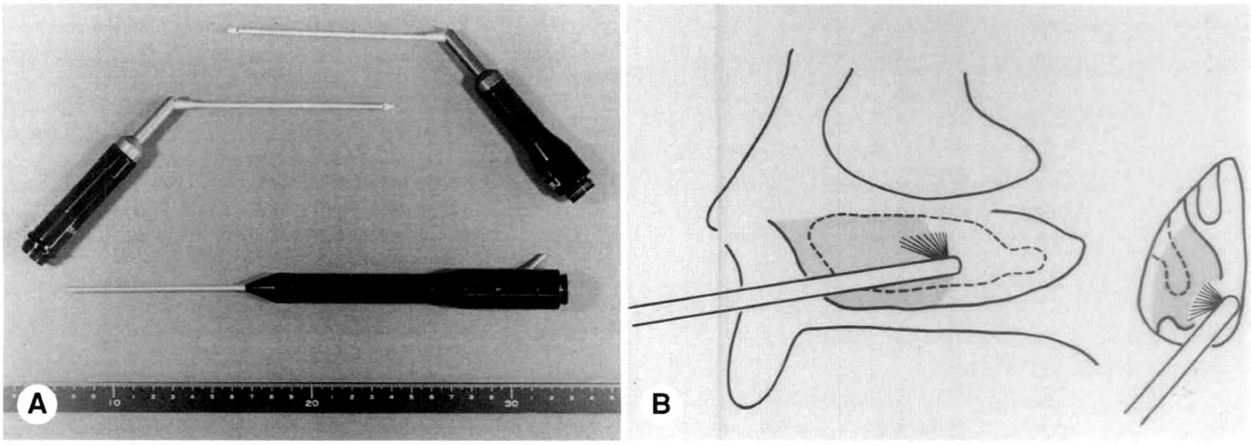

Fig 2. Carbon dioxide laser surgery. A) Handpiece. B) Surgical technique.

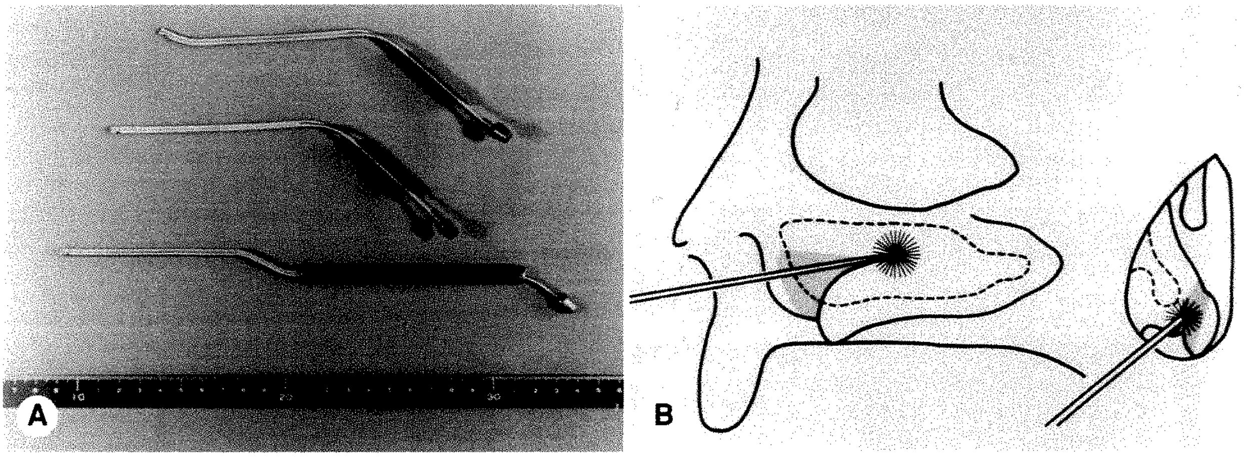

Fig 3. Potassium titanyl phosphate 532 laser surgery. A) Handpiece (curved type and straight type). B) Surgical technique.

pared nasal symptoms at the time of evaluation of short-term results and nasal symptoms at the present time (Table 4).

Fifty of the 96 patients completed the questionnaire (response rate: 52%), and the results were analyzed to investigate the long-term results of laser surgery.

TABLE 4. QUESTIONNAIRE

This questionnaire is for patients who received laser surgery for nasal allergy in our department more than 2 years ago. We request that you cooperate for future improvement in treatment.

1. I received the laser surgery on ____ ,19____
2. ____ weeks after surgery, I thought my symptoms had improved as follows:
   Sneezing
   Nasal discharge
   Nasal obstruction
   (Severe +++, Moderate ++, Mild +, No symptoms −)
3. After that, you did not visit our hospital. What is your present nasal condition? Check the appropriate relation.
   Sneezing Nasal discharge
   Nasal obstruction Better
   Unchanged (good condition after surgery continues)
   Worse (the condition returned to that before surgery)
4. For those who answered, "Worse" to Question 3, how long was the good condition maintained?
   Sneezing: About ___ months
   Nasal discharge: About ___ months
   Nasal obstruction: About ___ months
5. Are you receiving any treatment now? If you are, please give details.
   I am not receiving any treatment.
   I am receiving ________________
6. If you had the need, would you like to receive this surgery again?
   Yes No I don't know
7. If you have any suggestions or impressions, please give them below.

RESULTS

Changes in Nasal Mucosa After Surgery. Preoperatively, findings typical of nasal allergy, ie, watery nasal discharge adhering to a pale, swollen inferior turbinate, were observed in almost all cases. Immediately after surgery, carbonized black crusts and clots adhered to the surface of the inferior turbinate. Subsequently, fibrinous precipitation and exudate were observed for 1 to 2 weeks; then they gradually decreased and formed eschar. Subsequent findings showed that the eschar had fallen out and that epithelialization was almost complete in most cases. Two types of healing were seen: those in which the mucosal surface developed a pink color and was covered with slightly irregular granulation tissue (Fig 4), and those in which the mucosal surface was covered with relatively white and smooth cicatricial tissue (Fig 5). The volume of the inferior turbinate reduced remarkably, and watery nasal discharge decreased.

Histopathologic Findings. Among light microscopic findings (Fig 6), goblet cell hypoplasia was seen preoperatively in 31% (8/26), basal cell hyperplasia in 27% (7/26), and basement membrane hypertrophy in 46% (12/26). In the lamina propria mucosa, edema was observed in 81% (21/26), eosinophilic infiltration in 50% (13/26), enlargement of the nasal gland in 85% (22/26), and dilatation of sinusoidal capillaries in 65% (17/26).

Upon evaluation of the short-term results (4 to 10 weeks after surgery), epithelialization was completed and the nasal mucosa was covered with squamous epithelium in 52% (11/21) and with stratified cuboidal and/or stratified columnar epithelium in 29% (6/21); thus, more than 80% of the cases had nasal mucosa covered with an epithelium that was different from that of the preoperative pseudostratified, ciliated, columnar epithelium (Fig 7). In addition, many fibroblast masses involving capillary hyperplasia and col-

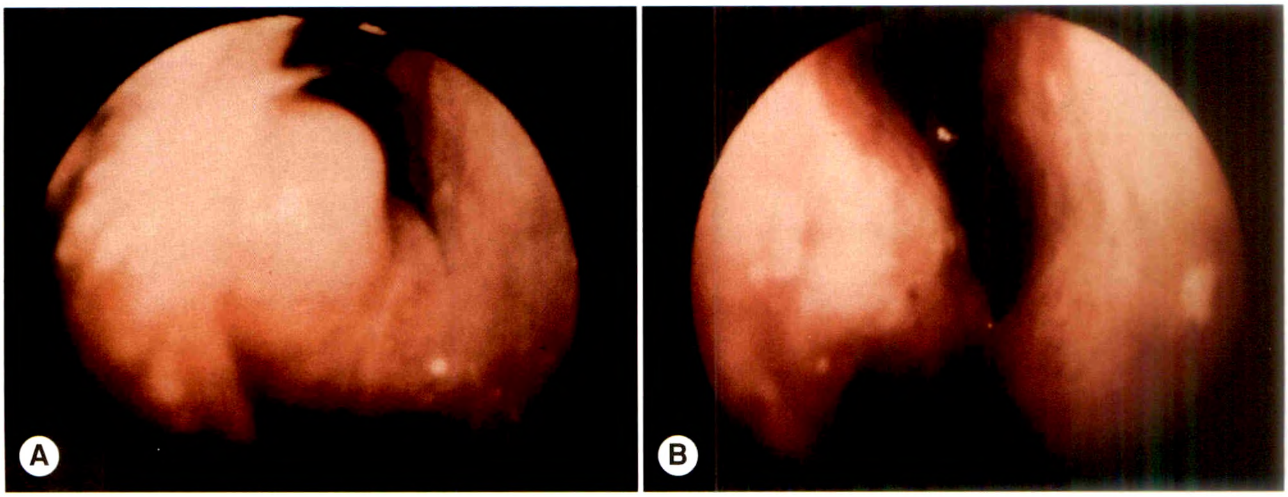

Fig 4. Case of nasal mucosa covered with granulation tissue after surgery. A) Before surgery. Nasal mucosa shows adhesion of watery discharge and severe swelling. B) Eight weeks after surgery. Surface of nasal mucosa is covered with granulation tissue, which is pale red and slightly irregular, and volume of concha nasalis inferior is markedly decreased.

lagenous fibers, ie, granulation tissue, and cicatricial tissue consisting of collagenous fibers alone replaced the lamina propria mucosa, respectively, in 67% (14/21) and 24% (5/21; Fig 8). Edema, eosinophilic infiltration, and enlarged nasal glands, which were found preoperatively in this layer, had almost completely disappeared.

The effects seen 4 to 10 weeks after surgery persisted for a long period (more than 2 years after surgery in nonrelapsed cases); substitution of stratified, squamatized epithelium and cicatricial tissue, mainly consisting of collagenous fibers in the lamina propria mucosa, was observed (Fig 9). Conversely, in cases in which long-term efficacy was not seen (relapsed cases), many goblet cells remained in the original pseudostratified, ciliated columnar epithelium, and typical mucosal findings of nasal allergy such as edema, eosinophilic infiltration, and enlarged nasal glands in the lamina propria mucosa were observed (Fig 10).

Among scanning electron microscopic findings, the surface of the normal nasal mucosa consisted of ciliated cells and nonciliated cells, the latter mainly being goblet cells (Fig 11). The changes in the surface microstructure of the lamina propria mucosa in nasal allergy included a decrease in ciliated cells, an increase in goblet cells, and also changes in the cilia themselves, which decreased in number and became shortened. The grades of change varied from an almost normal state to an extreme decrease in number of the ciliated cells and substitution by goblet cells (Fig 12). Mucosae with more macroscopically

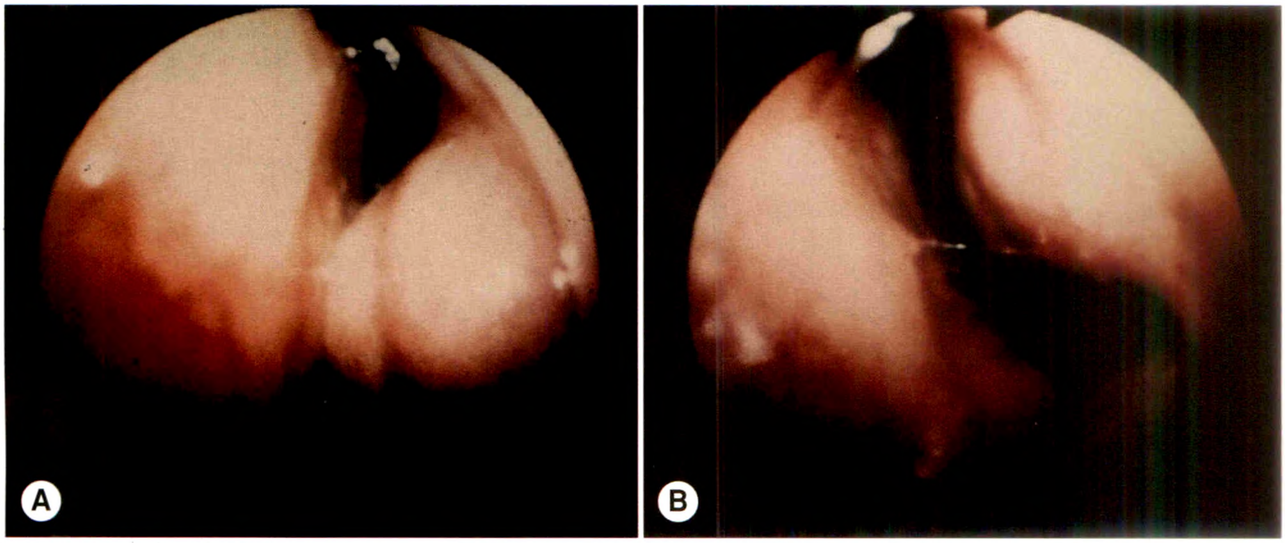

Fig 5. Case of nasal mucosa covered with cicatricial tissue after surgery. A) Before surgery. Pallor and marked swelling of concha nasalis inferior is seen. B) Nine weeks after surgery. Surface of nasal mucosa is covered with relatively white cicatricial tissue, whose surface is relatively smooth, and meatus nasi communis is sufficiently dilated.

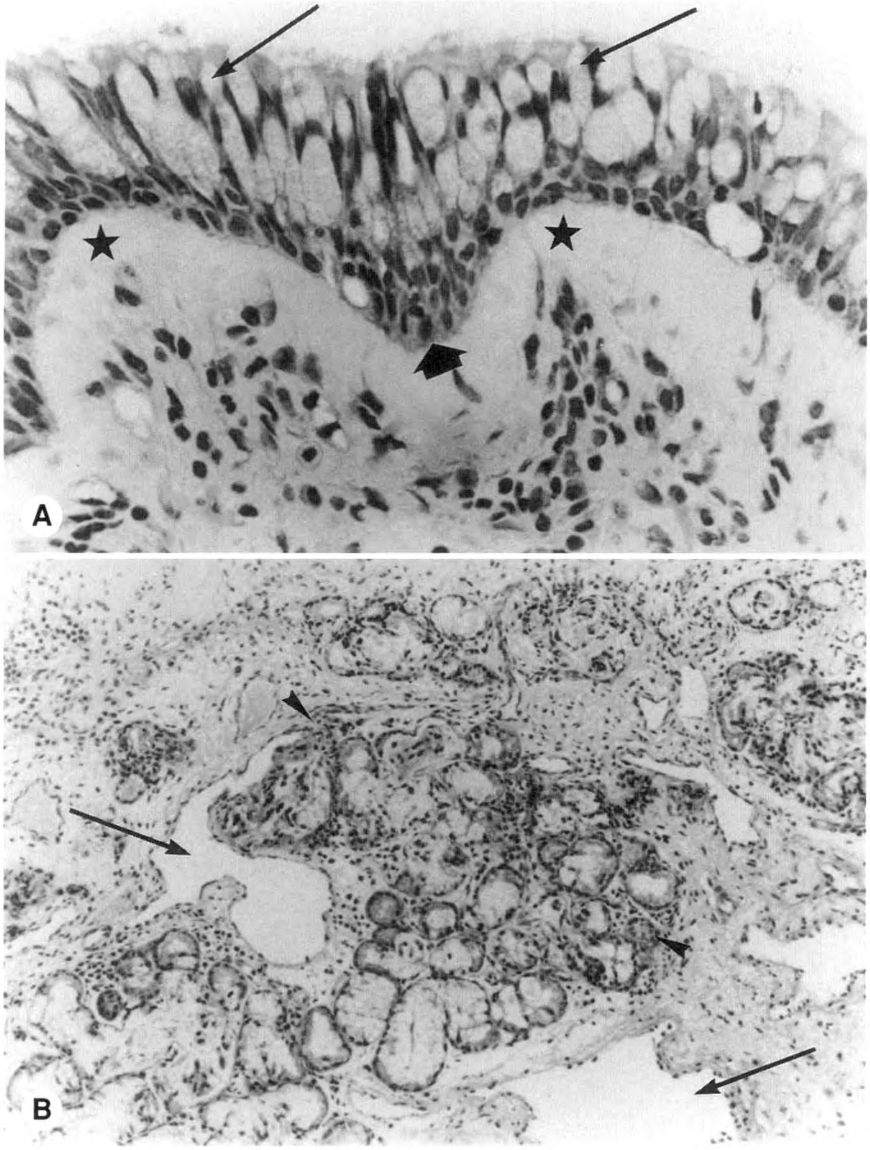

Fig 6. Light microscopic findings of nasal mucosa before surgery. A) In mucosal epithelium, hyperplasia of goblet cells (thin arrows) and basal cells (thick arrow) and hypertrophy of basement membrane (stars) are observed (original ×200). B) In lamina propria mucosa, edema, eosinophilic infiltration, enlargement of nasal gland (arrowheads), and dilatation of sinusoidal capillary (arrows) are seen (original ×100).

remarkable edematous changes had more severe changes of the same kind.

The regenerative epithelia of the nasal mucosa in cases judged to have effective results at short term (4 to 10 weeks after surgery) had no ciliated cells or goblet cells and were covered with squamous epithelia. Moreover, findings suggestive of regeneration of squamous epithelium were also recognized (Fig 13).

Observation of specimens from a second operation for cases in which the effect had disappeared upon evaluation of long-term results (more than 2 years after surgery) revealed that the epithelium of the nasal mucosa was not squamous epithelium, but respiratory epithelium composed of ciliated cells and goblet cells, which agreed with the light microscopic findings. In addition, a decrease in ciliated cells and an increase in goblet cells were confirmed (Fig 14).

The histopathologic changes found in the nasal mucosa before and after laser surgery are summarized in Table 5.

Changes in Grades of Nasal Ventilation. The changes in nasal resistance in the 45 cases in which nasal ventilation could be measured before and after laser surgery are shown in Fig 15. Before laser surgery, severe nasal obstruction with a nasal resistance of more than 0.75 Pa/cm^3 per second was observed in 27% (12/45), and moderate nasal obstruction with a nasal resistance of 0.50 to 0.75 Pa/cm^3 per second in 29% (13/45). After surgery, mild nasal obstruction with a nasal resistance of 0.25 to 0.50 Pa/cm^3 per second was confirmed in 67% (30/45), and a normal condition with a resistance of less than 0.25 Pa/cm^3 per second in 31% (14/45). The average preoperative resistance was 0.60 ± 0.09 Pa/cm^3 per second (mean ± SD), and postoperative resistance was 0.30 ± 0.09 Pa/cm^3 per second, showing a significant de-

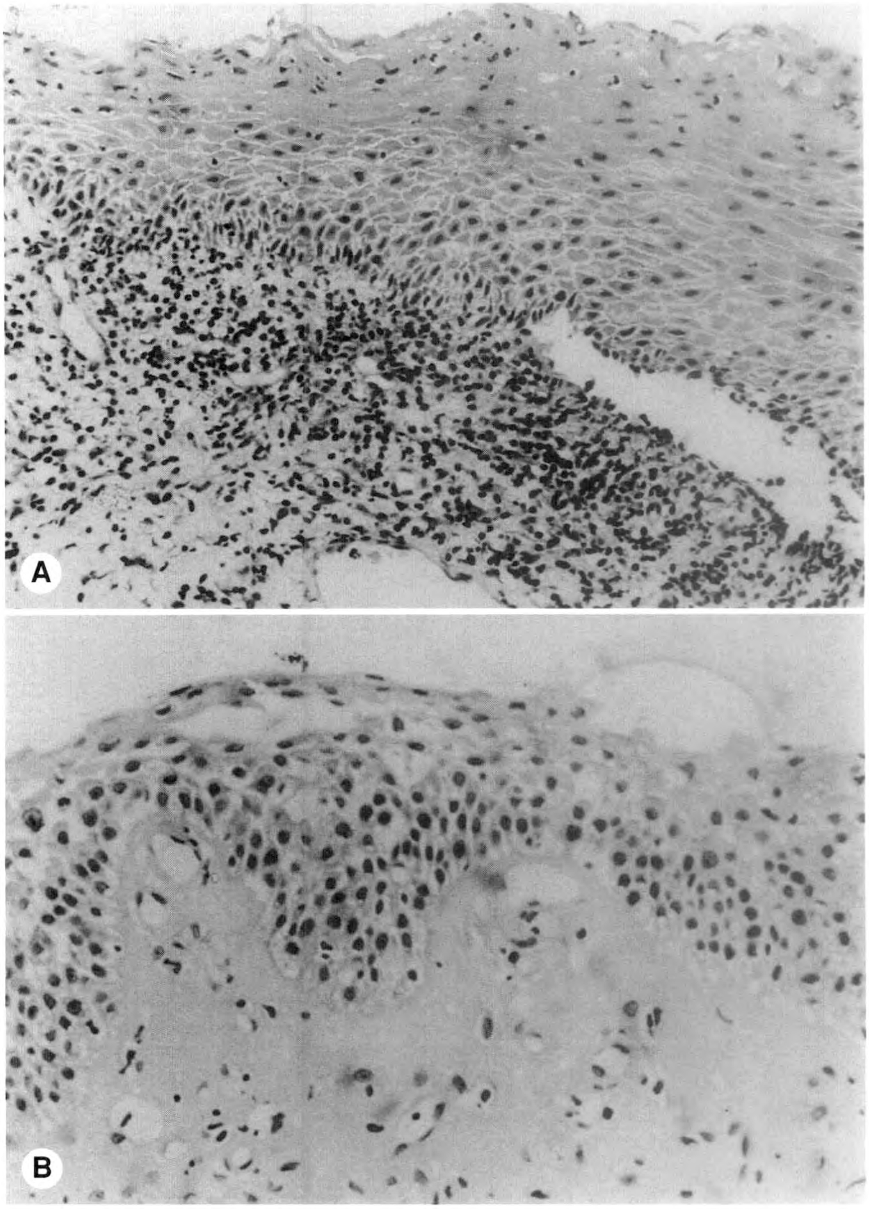

Fig 7. Light microscopic findings of mucosal epithelium of nose in short term after surgery (original ×200). A) Case with mucosa covered with squamatized epithelium (10 weeks after surgery). B) Case with mucosa covered with cuboidal or columnar epithelium, which was stratified (9 weeks after surgery).

crease ($p < .01$, Student's *t*-test).

Changes in Oxygen Partial Pressure in Lamina Propria Mucosa. The PO_2 of the nasal mucosa of the 12 normal volunteer controls was 66.2 ± 9.8 mm Hg (mean ± SD). In the 16 cases in which the PO_2 could be measured before and after surgery, it was 69.8 ± 6.9 mm Hg (mean ± SD) before surgery and 64.4 ± 16.4 mm Hg after surgery (Fig 16). There were no significant differences among the normal controls, preoperative cases, and postoperative cases (Student's *t*-test).

Surgical Results. The improvement rating of symptoms based on nasal allergy diaries is shown in Fig 17. The efficacy rate was 70% (83/119) for sneezing, 72% (120/166) for nasal discharge, and 91% (185/204) for nasal obstruction. Concerning the overall improvement rating, laser surgery was effective in 87% (177/204). In particular, nasal obstruction disappeared in 50% (102/204) and improved remarkably in 23% (46/204). These results were better than those for sneezing and nasal discharge ($p < .01$, histamine test).

The postoperative course of the 50 patients who responded to the questionnaire ranged between 26 and 62 months (mean 42.4 months). Of these 50 patients, 38 had received CO_2 laser surgery, and 12, KTP/532 laser surgery. Figure 18 presents the results of the questionnaire by comparing the short-term nasal results. There was no difference in nasal symptoms in cases in which efficacy persisted (nonrelapsed cases), including those judged as better or unchanged; ie, efficacy persisted in 81% (26/32) with regard to sneezing, 78% (32/41) for nasal discharge, and 76% (38/50) for nasal obstruction. These nonre-

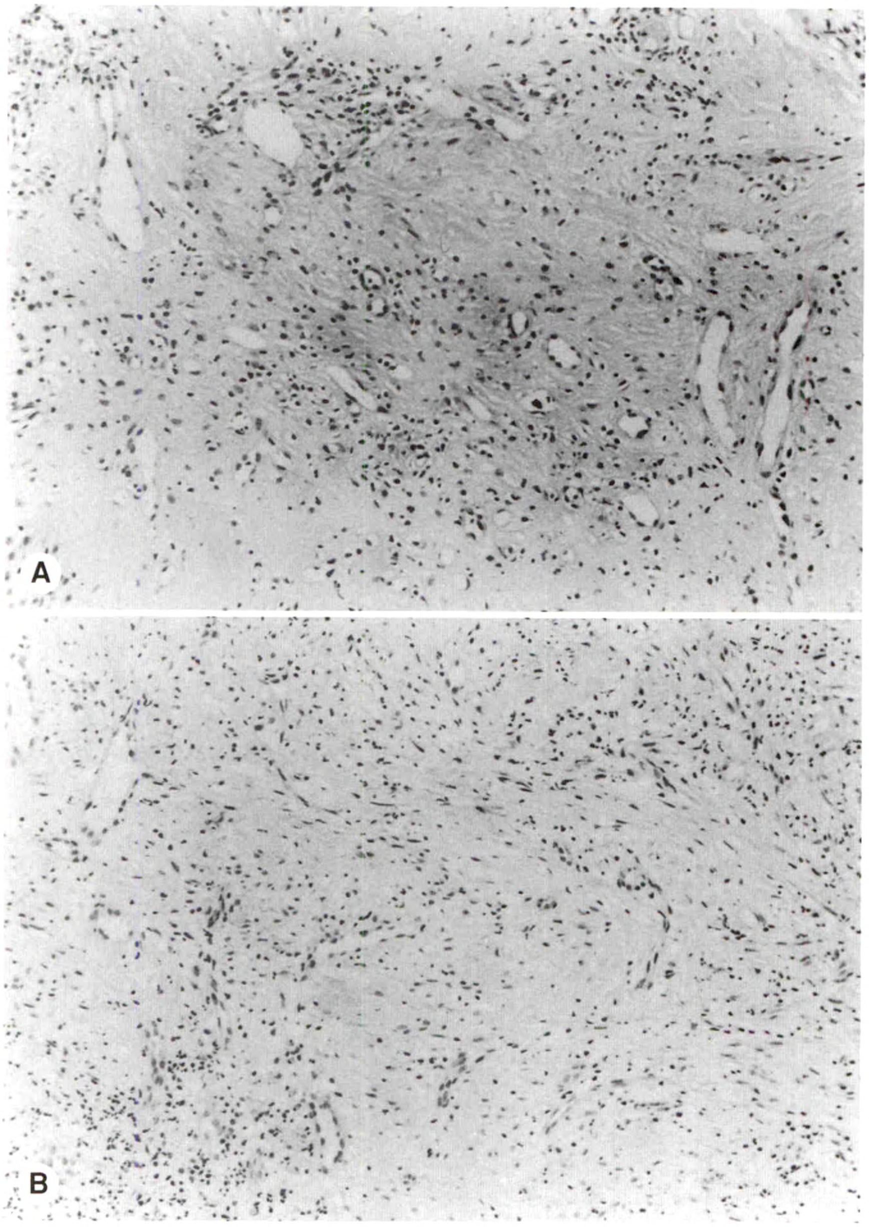

Fig 8. Light microscopic findings of lamina propria mucosa shortly after surgery (original ×100). A) Case with substituted granulation tissue (8 weeks after surgery). B) Case with substituted cicatricial tissue (8 weeks after surgery), in which poor vascularization and collagenous fibers are found as main components.

lapsed cases received no combined therapy such as oral drugs, nasal drops, etc, after laser surgery. However, a relapse with regard to individual symptoms was confirmed in 19% to 24% of the cases, and the period until relapse was less than 6 months in 50% (3/6), and 6 to 12 months in 50% (3/6) for sneezing; less than 6 months in 33% (3/9), 6 to 12 months in 44% (4/9), and more than 12 months in 22% (2/9) for nasal discharge; and less than 6 months in 25% (3/12), 6 to 12 months in 42% (5/12), and more than 12 months in 33% (4/12) for nasal obstruction.

DISCUSSION

Mechanism of Laser Surgical Treatment for Allergic Rhinitis. We studied how laser surgery causes the disappearance or relief of symptoms of nasal allergy. First, there is an absolute decrease in the volume of the inferior turbinate vaporized or excised by laser, by which nasal obstruction may be relieved. This point was proven by findings before and after surgery, and the results of the nasal ventilation test also support this concept.

Nasal ventilation tests are roughly divided into anterior and posterior methods. The former is a convenient standard method,[3] in spite of the disadvantages that a totally obstructed nasal cavity cannot be measured, that bilateral cavities cannot be measured simultaneously, etc. Moreover, in the nasal ventilation test, a comparison of resistances at a certain pressure standard is required, and internationally, p = 150 Pa is defined as the standard, although in Japan, p = 100 Pa is generally defined as the standard. In this study, we used the anterior method with a mask and measured the total nasal resistance during inspira-

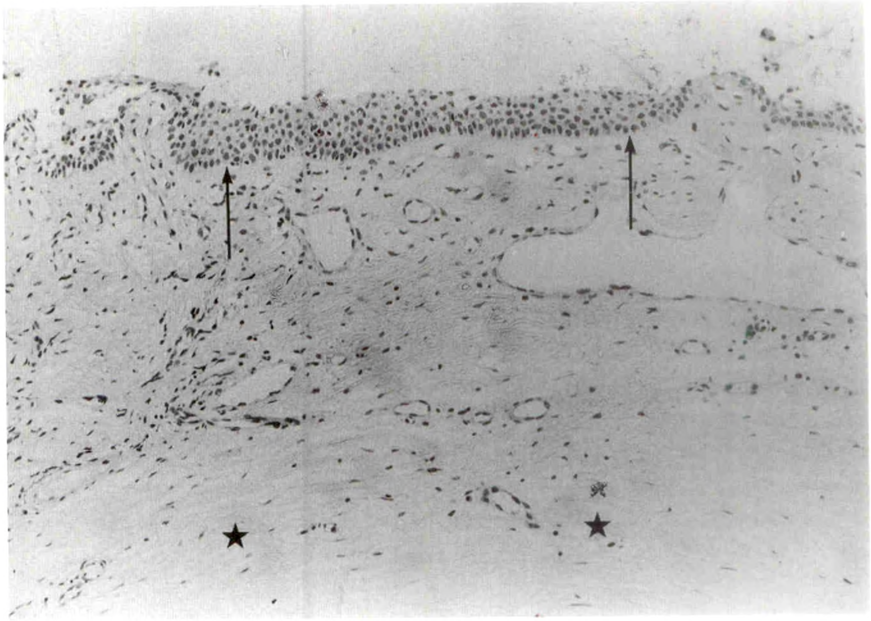

Fig 9. Light microscopic findings in nasal mucosa 46 months after surgery (non-relapsed case; original ×33). Shows squamatized epithelium (arrows) and lamina propria mucosa with cicatricial tissue (stars), mainly composed of collagenous fibers.

tion using p = 100 Pa as the standard. In the majority of cases, the subjective improvement rating of nasal obstruction was consistent with changes in nasal resistance, suggesting that this nasal ventilation test might sufficiently reflect improvements in nasal obstruction.

Second, decreases in goblet cells in the mucosal epithelium and the nasal gland present in the lamina propria mucosa are proven by changes in light microscopic findings of the nasal mucosa observed before and after laser surgery, and may relieve the watery discharge.

Third, suppression of allergic reactions due to squamatization of the mucosal epithelium is indicated. Unlike the original stratified ciliated epithelium, postoperatively regenerating mucosal epithelium has become metaplastic or consists of stratified cuboidal or columnar cells, which is assumed to make invasion by antigens under the epithelium difficult, thereby suppressing the progress of an allergic reaction, even though the antigens in the air are absorbed into the mucous layer and adhere to the nasal mucosa. In a study on CO_2 laser surgery, Fukutake et al[4] investigated changes in thresholds in provocation tests of the nasal mucosa and of eosinophils in nasal discharge in 34 cases that showed favorable results 1 year after surgery, and reported that an increase in threshold and a decrease in eosinophils were shown by the provocation test after surgery and that histologic changes of the superficial layer of the nasal mucosa due to laser surgery suppressed the antigen-

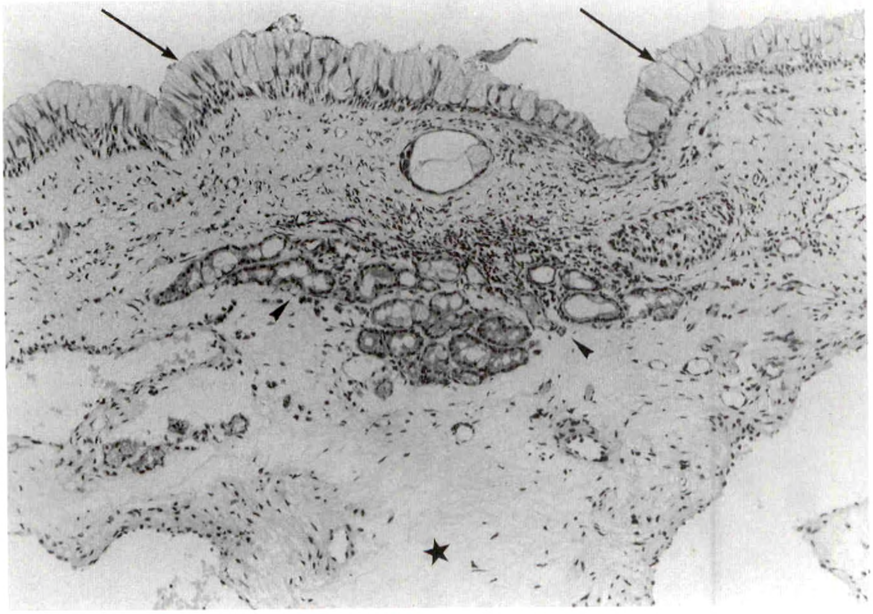

Fig 10. Light microscopic findings 54 months after surgery (relapsed case; original ×33). Mucosal epithelium is columnar, pseudostratified, ciliated epithelium that has many goblet cells (arrows), and there are findings typical of nasal allergy, including edema (star), eosinophilic infiltration, and enlargement of nasal mucosa (arrowheads).

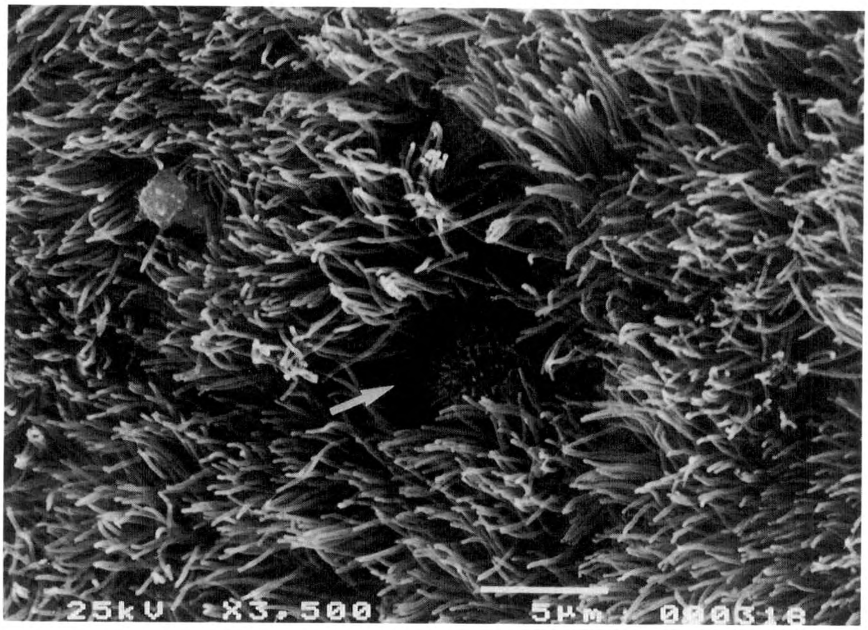

Fig 11. Scanning electron microscopic findings in normal nasal mucosa. In normal nasal mucosa, cells seen on surface are mainly ciliated cells and goblet cells (arrow). (Majority are ciliated cells.)

antibody reaction. Further, Kawamura et al,[5] who also performed CO2 laser surgery, investigated increases and decreases in eosinophilic cationic protein (ECP) in irrigation solution due to the provocation of antigen before and after surgery, and confirmed a decrease in ECP in the group in which the symptoms improved, indicating suppression of release of a chemical mediator associated with squamatization of the epithelium of the nasal mucosa as one of the factors in the effectiveness of laser surgery. The findings of both of these studies are consistent with our experience.

Fourth, cicatrization of the lamina propria mucosa is indicated. In the course of wound healing after laser surgery, edematous lamina propria mucosa may be replaced over a long period by cicatricial tissue consisting of dense collagenous fibers, via granulation tissue caused by frequent vascularization and fibroblasts. This can make development of edema in the lamina propria mucosa difficult, even during exposure to antigens, resulting in the relief of nasal obstruction.

We measured PO2 in the nasal mucosa in some cases to investigate hemodynamics, which possibly participate in the swelling and the color of the nasal mucosa. There was no significant difference in PO2 between the normal group and the preoperative nasal allergy group, and there was no definite trend in the diverse cases, including those with increased or decreased PO2 after surgery, and no significant differences were found after surgery. Concerning the hemodynamics of the nasal mucosa before and after laser surgery, Tomoda et al[6] measured indicators of the local hemoglobin level of the nasal mucosa (IHb) using the reflection spectrum method and reported that the IHb in patients with nasal allergy was significantly decreased compared to that in normal volunteers before surgery, but returned to a normal level after surgery. Moreover, they reported that an improvement in the hemodynamics of the nasal mucosa was observed, and vascularization was confirmed histopathologically in the superficial layer of the lamina propria mucosa. In addition, by measuring blood flow volume on the mucosal surface using a laser Doppler method, Kawamura et al[5] reported that blood flow volume in the nasal mucosa in patients with nasal allergy was significantly decreased compared to that in normal volunteers before surgery, and tended to further decrease after surgery. They considered that blood flow in the nasal mucosa decreased due to ischemia, and that interstitial edema might be further decreased because of the substitution of poorly vascularized cicatricial tissue. Oxygen partial pressure, IHb, and blood flow volume of the nasal mucosa could all be indicators representative of the hemodynamics of the nasal mucosa, although these parameters are not comparable. However, the results of our study differed from those reported by the above researchers. One reason was individual differences in wound healing of the nasal mucosa observed during postoperative measurement. Namely, the PO2 of the nasal mucosa investigated in this study was presumed to increase after surgery in cases in which the lamina propria mucosa consisted of juvenile granulation tissue accompanied with abundant vascularization, but to decrease after surgery in cases in which the lamina propria mucosa started to change into cicatricial tissue with poor vascularization. The nasal mucosa has an anatomically unique vascular system consisting

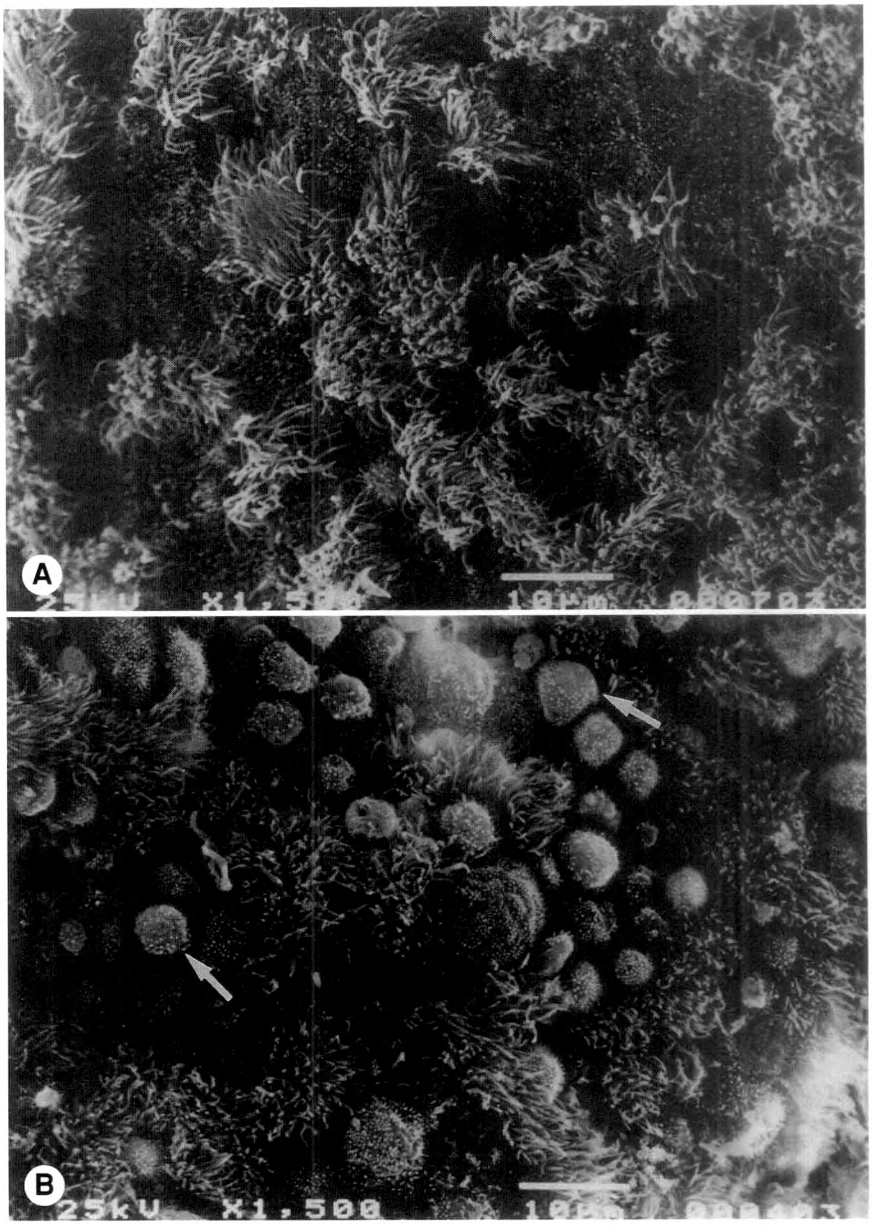

Fig 12. Scanning electron microscopic findings in nasal mucosa before surgery. A) Scattered decreases in ciliated cells. B) Severe changes, with remarkable increase in goblet cells (arrows) and decrease in cilia.

of loop capillaries near the mucosal surface, deep sinusoidal capillaries in which there is a large volume of blood, and arteriovenous anastomosis, and its hemodynamics still remain to be determined because of differences in measurement methods, particularly in the depth at which measurement is performed.

The fifth point is that degeneration of the sensory and autonomic nerves in the nasal mucosa due to the thermal effects of the laser is suggested. This might reduce the sensitivity of the nasal mucosa, resulting in relief from nerve-mediated nasal symptoms, particularly sneezing attacks and watery discharge. Yao et al,[7] who performed chemical cautery with trichloroacetic acid on the inferior turbinate, indicated that its action caused dysfunction of nerve conduction. Adrenergic and cholinergic nerve fibers are abundantly present in the lamina propria mucosa, and laser surgery can be expected to have a degenerative effect on the nerve fibers of the nasal mucosa similar to chemical cautery and electrocoagulation. The fact that laser surgery is also effective for vasomotor rhinitis, which is considered to be a hypersensitivity of the autonomic nerves of the nasal mucosa,[8,9] might clinically support the idea that degeneration of the sensory and autonomic nerves in the nasal mucosa is due to the thermal effects of the laser.

Although these changes are not specific to laser surgery, they are recognized most distinctly in laser surgery (Table 6).

Techniques of Laser Irradiation. Laser surgery techniques for nasal allergy can be generally classified into vaporization and excision of the mucosa of

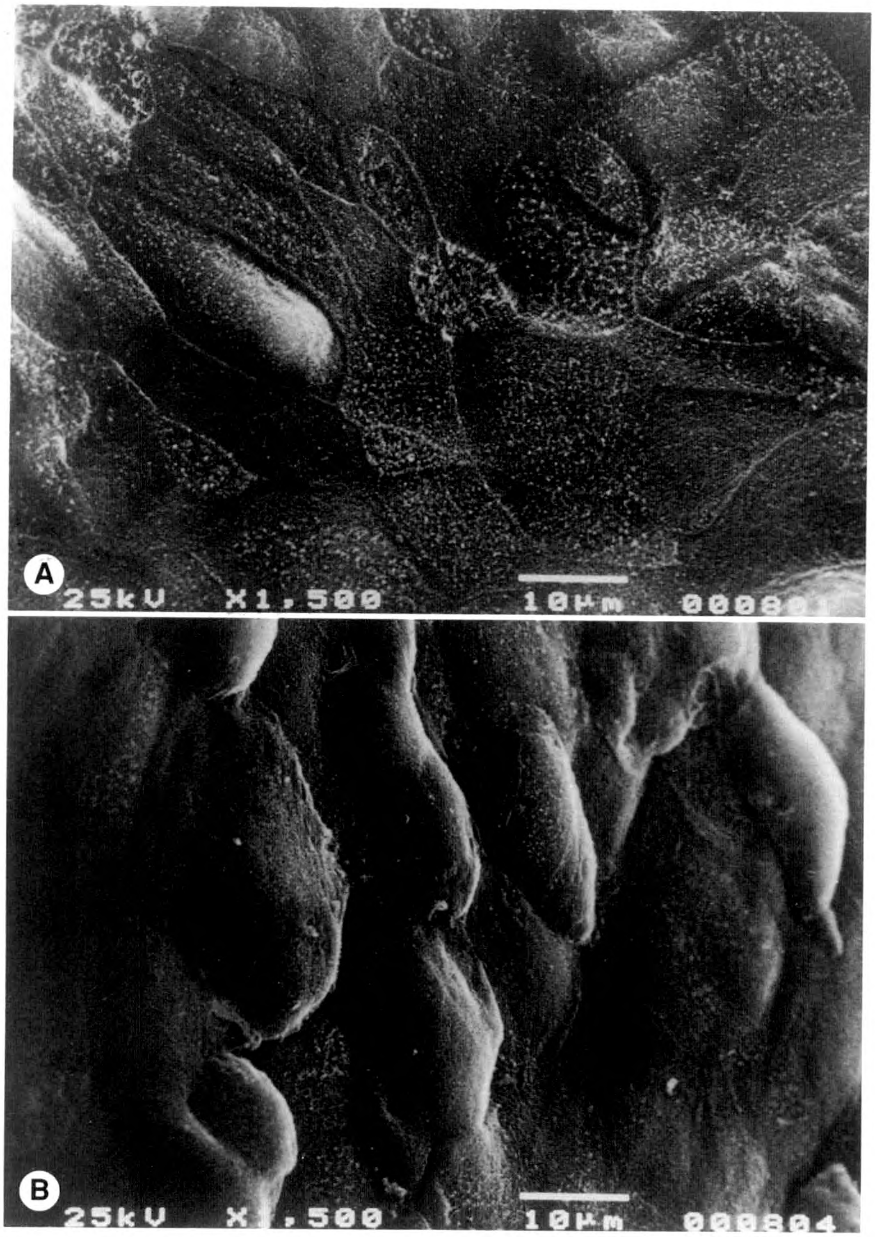

Fig 13. Scanning electron microscopic findings in nasal mucosa shortly after surgery (effective). A) Regenerated membrane is covered with squamous epithelium (10 weeks after surgery). B) Findings suggestive of regenerative process due to squamous epithelium are also observed (8 weeks after surgery).

the concha nasalis inferior.

To vaporize the mucosa of the inferior turbinate, a CO2 laser with low reflectance and a low diffusion coefficient and high absorptive power is used. Mittelman[10] performed vaporization using a power of 6 to 10 W with defocused beams of 1 to 2 mm, Selkin[11] used a 15- to 18-W continuous wave with a combination of focused and defocused beams, and Elwany and Harrison[12] performed vaporization using 20- to 30-W defocused beams. In Japan, Fukutake et al[4] used 20-W, 0.1-second–pulse wave defocused beams, and Kubota[13] used 8- to 22-W, 0.5-second–pulse wave defocused beams. We used defocused beams with an output of 15 W, equivalent to the conditions described above, while using a continuous mode to reduce surgical time by vaporizing as large an area as possible at one time. While some feel that using a continuous mode requires skill, in our cases there was no mis-irradiation, which could possibly cause clinical problems after using the continuous mode. Moreover, there were no cases of continuous-wave laser irradiation causing increased hemorrhage or necrosis of the turbinate bone, and irradiation was performed safely. Concerning the number of surgeries performed, Mittelman[10] and Selkin[11] performed laser surgery only once, while Fukutake et al[4] performed surgery once a week for 5 weeks. Kubota[13] reported that more than 80% of the cases required surgery only once, or at most twice, and indicated that the necessity for additional irradiation depended on the severity and postoperative improvement rating of the individual cases. While we try to obtain sufficient space in the lumen by vaporizing as large

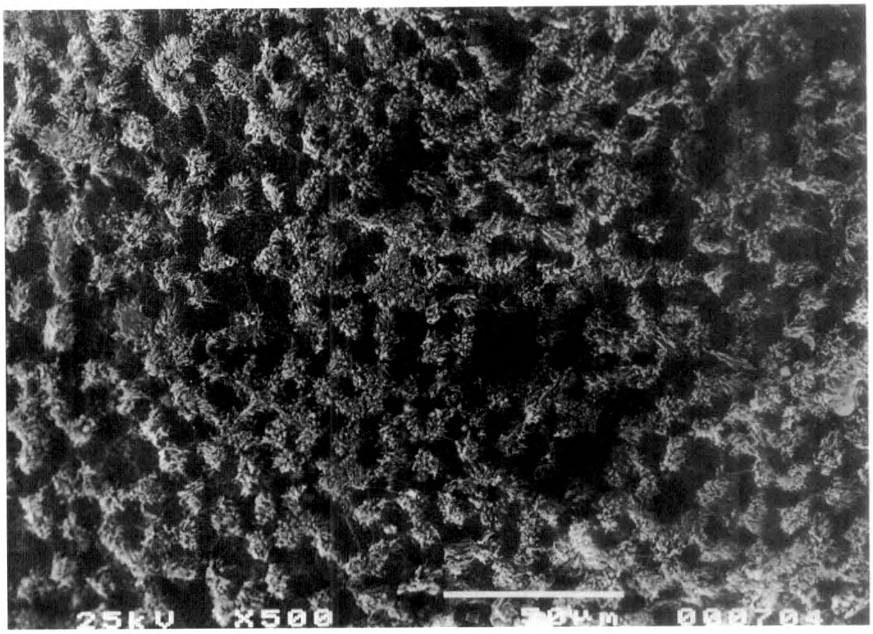

Fig 14. Scanning electron microscopic findings in nasal mucosa 38 months after surgery (relapsed case). Mucosal epithelium is not squamous, but respiratory epithelium, and decrease in ciliated cells and increase in goblet cells are found.

an area as possible at one time, we perform 1 procedure and then follow-up. While there is a tendency for the duration of nasal obstruction or nasal discharge as postoperative reactivity to be prolonged, ie, 1 to 2 weeks, compared to staged irradiation, the number of hospital visits is decreased.

To excise the mucosa of the inferior turbinate, it is best to use a laser that has excellent coagulability and can be used for contact irradiation, in addition to having surgical instruments of as small a diameter as possible. While the neodymium:yttrium-aluminum-garnet (Nd-YAG) laser has been frequently used in the clinical field, we use the KTP/532 laser. This laser has a green visible beam with a wavelength of 532 nm obtained by passing Nd-YAG laser beams through a KTP crystal and exhibits good excision and coagulation features. The beam is passed through small-diameter quartz fibers for contact or noncontact irradiation. Our KTP/532 laser achieved satisfactory excision of the mucosa of the inferior turbinate with little bleeding under conditions of 7 to 10 W and continuous wave output.

The purpose of vaporizing or excising the mucosa of the inferior turbinate is to decrease the area of nasal mucosa that is the site of allergic reaction, causing coagulative degeneration through the thermal effects of the laser. In that sense, both the CO_2 laser and the KTP/532 laser achieve the same purpose, but the latter is considered to be easier to use to treat the nasal mucosa. As for postoperative wound heal-

TABLE 5. HISTOPATHOLOGIC CHANGES IN NASAL MUCOSA

	Preoperative Findings (n = 26)	*Short-term Findings (n = 21)*	*Long-term Findings*
Light microscopy			
Epithelium of nasal mucosa	Hyperplasia of goblet cells in 8	Squamous metaplasia in 11	Nonrelapsed cases (n = 3): stratified squamous epithelium
	Hyperplasia of basal cells in 7	Stratified cuboidal or columnar epithelium in 6	Relapsed cases (n = 5): ciliated columnar epithelium
	Hyperplasia of basement membrane in 12	Ciliated columnar epithelium in 4	
Lamina propria mucosa	Edema in 21	Granulation tissue in 14	Nonrelapsed cases: scar tissue composed of collagen fibers
	Eosinophilic infiltration in 13	Scar tissue in 5	Relapsed cases: edema, eosinophilic infiltration, enlarged nasal gland
	Enlarged nasal gland in 22	Almost normal in 2	
	Dilated sinusoid vein in 17		
Scanning electron microscopy	Decrease of ciliated cells and increase of goblet cells, shortening of cilia	Squamous epithelium or regenerative process by squamous epithelium	Relapsed cases: respiratory epithelium composed of ciliated and goblet cells

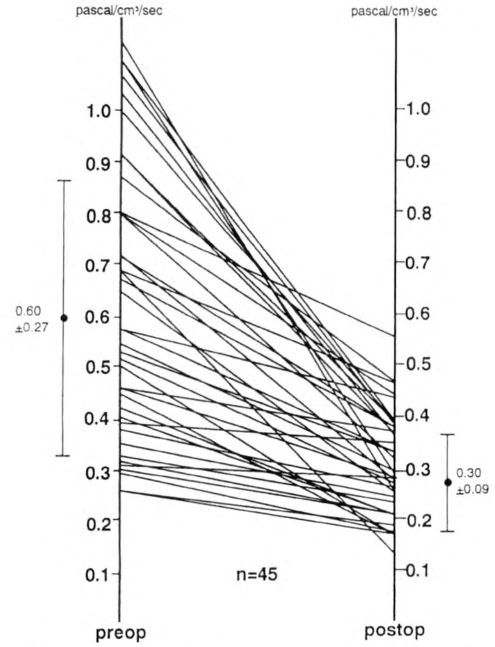

Fig 15. Changes of nasal resistance. Postoperative nasal resistance was significantly decreased ($p < .01$, Student's *t*-test).

ing of the nasal mucosa, the fact that CO2 laser–treated cases required 4 to 6 weeks and KTP/532 laser–treated cases required 8 to 10 weeks suggests a tendency for healing to be delayed for 2 to 6 weeks when the KTP/532 laser is used.

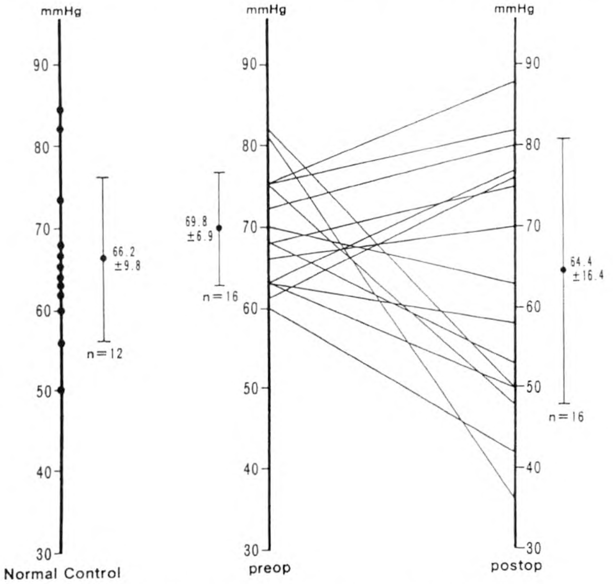

Fig 16. Changes of oxygen partial pressure of lamina propria mucosa. At left is oxygen partial pressure of lamina propria mucosa in normal control group (n = 12). At right are changes in oxygen partial pressure of lamina propria mucosa in patients (n = 16) before and after surgery. There were no significant differences among normal controls, preoperative group, and postoperative group (Student's *t*-test).

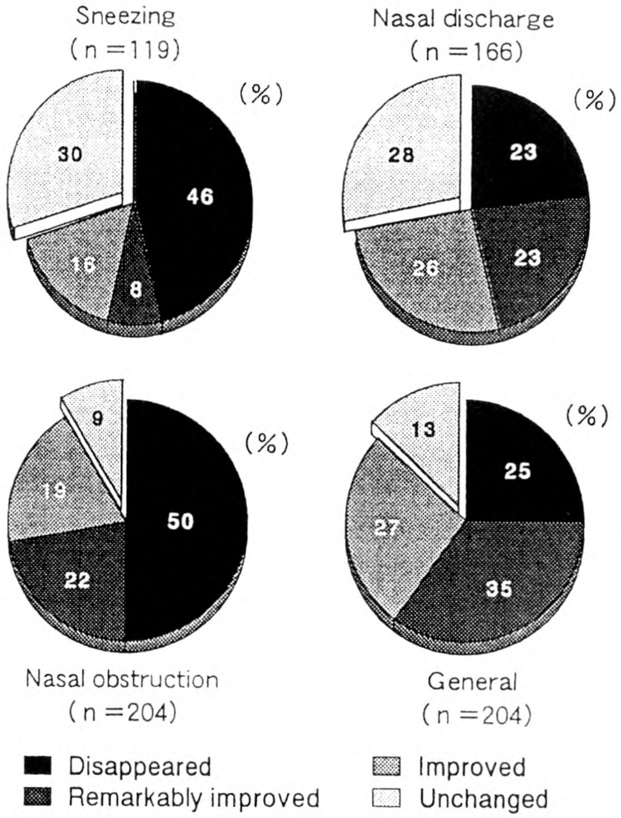

Fig 17. Short-term results of laser surgery. Efficacy rate for each symptom was 70% for sneezing, 72% for nasal discharge, and 91% for nasal obstruction.

Comparison With Other Surgical Approaches. The surgical methods performed at present for the treatment of nasal allergy are roughly classified into transection of the autonomic nerve innervating the nasal mucosa, eg, vidian neurectomy, and various types of surgery on the mucosa of the inferior turbinate.

Vidian neurectomy complications include a decrease in lacrimal gland secretion, palatal hypoesthesia, and trismus. It has been reported that although this method has good effects on nasal discharge and sneezing, nasal obstruction does not completely dis-

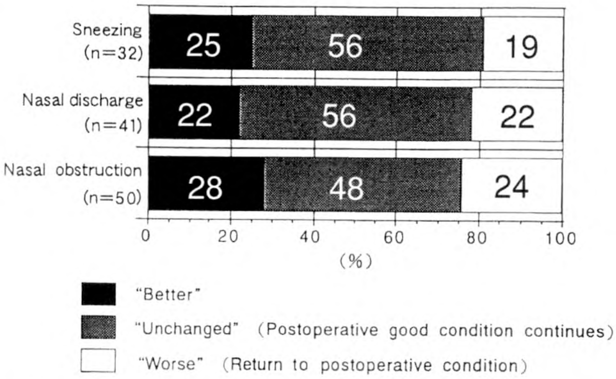

Fig 18. Long-term results of laser surgery. Mean postoperative period in 50 cases was 42.4 months, and surgical effect persisted in 81% for sneezing, 78% for nasal discharge, and 76% for nasal obstruction.

TABLE 6. COMPARISON OF MECHANISMS OF ACTION AMONG VARIOUS SURGICAL TREATMENTS

	Reduction of Turbinate Volume	*Decrease of Nasal Gland*	*Stratification and Squamatization*	*Cicatrization of Lamina Propria*	*Degeneration of Mucosal Nerve*
Laser surgery	+	+	+	+	+
Global turbinectomy	+	+	+	±	±
Electrocoagulation	±	+	−	+	+
Chemical cautery	±	±	+	±	+

+ — effective; ± — slightly effective; − — ineffective.

appear in cases with hyperplasia of the lamina propria mucosa, and there are individual differences in the reduction of nasal mucosa edema. As a result, the indications for this procedure are limited.

The various types of mucosal surgery include inferior turbinectomy, electrocoagulation, cryosurgery,[14] chemical cautery, laser surgery,[10-12] etc. Despite the different methods being used at different institutions, similar short-term results have been obtained, that is, 80% to 100% improvement for nasal obstruction and 70% to 90% for overall improvement, as shown in Table 7.[7,10,11,14-17] However, inferior turbinectomy is complicated by marked bleeding, and postoperative use of intranasal tampons is essential. Moreover, children require general anesthesia; therefore, the physical, temporal, and financial burdens placed on patients may be considerable. Electrocoagulation is frequently accompanied by a considerable sensation of heat during surgery. Postoperative hemorrhage, crust formation, and bone necrosis of the inferior turbinate are also complications. Moreover, because an electrode is inserted under the mucosa, completion of coagulation during surgery cannot be confirmed.

Cryosurgery has the postoperative complication of severe swelling of the mucosa, which persists for 1 week. In addition, simultaneous bilateral surgery can cause cartilaginous necrosis or perforation of the nasal septum. In chemical cautery of the inferior turbinate, the depth the drug reaches is only 80 to 120 μm.

The complications of laser surgery — hemorrhage and the degree of pain during surgery — are mild compared to those of other treatments. It can be performed relatively safely and easily in the outpatient clinic, and does not require tampons. In our cases, 22% of the subjects (44/204) were children under 15 (in this age group nasal allergies are rapidly increasing). One to 2 weeks after laser surgery, transient reactive nasal obstruction and nasal discharge appeared, but as a rule, these did not require treatment. Further, there were no complications such as airway infections or hyposmia or crust formation due to necrosis of the periosteum or bone of the inferior turbinate. Although laser surgery has the disadvantage of requiring large and expensive apparatus, smaller and relatively inexpensive equipment has recently been made available to more clinicians.

Long-term Results and Relapse. The long-term results of surgical treatment are presented in Table 8.[4,16,17] Otsuka,[16] who performed large excisions of the nasal mucosa, reported that follow-up for 2 years after surgery showed an efficacy rate of 88% for nasal obstruction in outpatients, but that the results of questionnaires from 48 cases more than 5 years after surgery demonstrated an efficacy rate of about 70%, indicating an 18% decrease.

Fukutake et al[4] reported that a relapse in rhinitis occurred at 9 to 12 months after laser surgery in 15% of 40 cases (6/40) followed up 1 year after surgery, but the relapse was relieved by further surgery in all cases. They considered that relapse might be caused by insufficient initial laser irradiation. Kawamura et al[17] reported, on the basis of the results of questionnaires from 45 cases followed up for more than 2

TABLE 7. COMPARISON OF SHORT-TERM RESULTS OF SURGICAL TREATMENTS

				Efficacy Rate According to Symptoms (%)			
Method	*Authors*	*Date*	*No. of Cases*	*Sneezing*	*Nasal Discharge*	*Nasal Obstruction*	*Overall Improvement (%)*
Global turbinectomy	Takahashi[15]	1978	33	56	43	84	
	Otsuka[16]	1988	68	56	48	93	
Cryosurgery	Ozenberger[14]	1970	46		92	100	
Chemical cautery	Yao et al[7]	1988	50			86	
Laser surgery	Mittelman[10]	1982	30			100	
	Selkin[11]	1985	34			100	
	Kawamura et al[17]	1993	365				77
	Present report		204	70	72	91	87

TABLE 8. COMPARISON OF LONG-TERM RESULTS OF SURGICAL TREATMENTS

				Efficacy Rate According to Symptoms (%)				
Method	*Authors*	*Date*	*No. of Cases*	*Sneezing*	*Nasal Discharge*	*Nasal Obstruction*	*Overall Improvement (%)*	*Remarks*
Global turbinectomy	Otsuka[16]	1988	48	30	42	70		Questionnaire, >5 y after surgery
Laser surgery	Fukutake et al[4]	1988	40				76	Follow-up, >1 y after surgery
	Kawamura et al[17]	1993	45				76	Follow-up, >2 y after surgery
	Present report		50	80	78	76		Questionnaire, >2 y after surgery

years after laser surgery and 22 cases for more than 3 years after surgery, that if cases were judged to be effective at 1 month after surgery, the effect generally persisted for 2 to 3 years, but nevertheless, there was a small percentage of relapsed cases. Further, Mittelman[10] confirmed relapse in rhinitis in 10% (3/30) during a follow-up period of 3 to 11 months and considered that this might be due to insufficient vaporization. Selkin[11] described relapse in rhinitis in 21% (7/34) 6 to 12 months after surgery, but 3 cases were relieved by further surgery, and 4 cases by anti-allergy nasal drops that had been ineffective before surgery.

In our cases, concerning nasal obstruction, which had the highest short-term efficacy rate, 12 of 50 cases (24%) were considered to have relapsed. We compared the background factors of the 12 relapsed cases and the nonrelapsed group of 38 cases, in which efficacy persisted for more than 2 years. First, as shown in Fig 19, there were no significant differences in sex and age (χ^2 test) and, as shown in Fig 20, no significant differences in the short-term improvement rating (histamine test). However, the relapsed group tended to have more preoperatively severe cases (Fig 21).

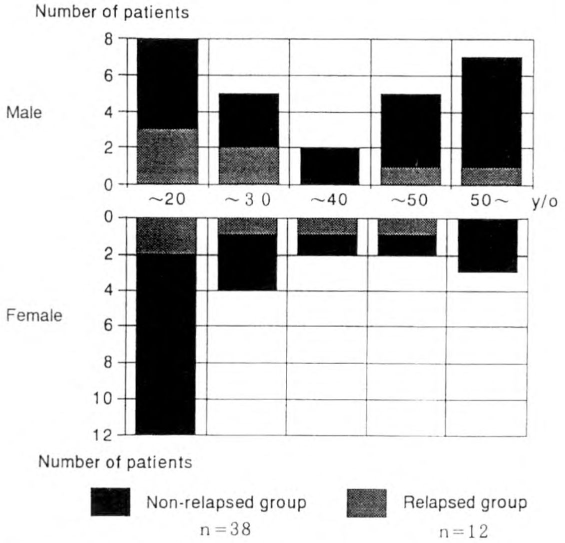

Fig 19. Composition of sexes and ages in group receiving evaluation of long-term results. There were no significant differences in sex or age between groups (χ^2 test).

There are still problems concerning the long-term results of laser surgery, so we used a questionnaire to investigate them. As with other surgical treatment, relapse occurs in some cases treated by laser surgery. The relapse suggests limits to surgical treatment alone for nasal allergy. In laser surgery, combination with medical treatment should be considered to prevent relapse and improve long-term results.

CONCLUSIONS

Morphological changes before and after laser surgery in patients with perennial nasal allergies were observed by light microscopy and by scanning electron microscopy as follows. Hyperplasia of the mucosal epithelium, mainly involving goblet cells and basal cells, hypertrophy of the basement membrane, edema of the lamina propria mucosa, eosinophilic infiltration, enlargement of the nasal gland, and dilatation of the sinusoidal capillary, etc, were observed preoperatively. After laser surgery, the mucosa was covered by squamatized, cuboidal, or stratified columnar epithelium. Granulation tissue or cicatricial tissue was found, but edema, eosinophilic infiltration, and enlarged nasal glands had all but disappeared in the lamina propria mucosa.

To objectively evaluate short-term improvement of nasal obstruction by laser surgery, a nasal ventilation test was performed before and after surgery. Na-

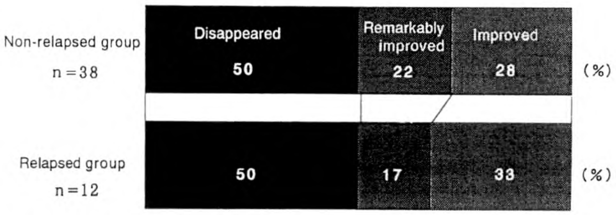

Fig 20. Short-term improvement. There was no significant difference in improvement rating between groups.

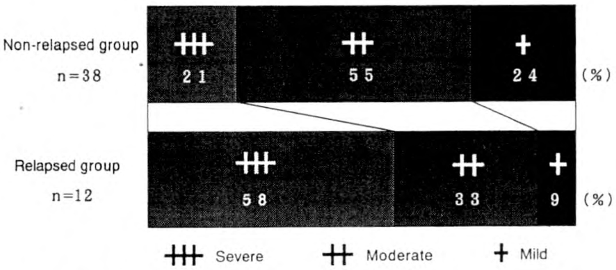

Fig 21. Preoperative severity and relapse. Preoperatively severe cases tended to be more frequent in relapsed group.

sal resistance was 0.60 ± 0.09 Pa/cm^3 per second before surgery and 0.30 ± 0.09 Pa/cm^3 per second after surgery, showing a significant decrease ($p < .01$, Student's *t*-test).

Changes in hemodynamics in the nasal mucosa evaluated by oxygen consumption showed no significant short-term improvement.

Laser surgery for nasal allergy causes 1) an absolute decrease in inferior turbinate volume, 2) decreases in goblet cells and nasal glands, 3) suppression of allergic reaction by stratified squamatization of the nasal mucosa epithelium, 4) substitution of granulation-like tissue and cicatricial tissue for the lamina propria mucosa, and 5) degeneration of the sensory and autonomic nerves of the nasal mucosa.

Between June 1986 and November 1995, laser surgery was performed in 204 cases of refractory perennial allergic rhinitis. According to the short-term results (4 to 10 weeks after surgery), laser surgery was effective in 70% (83/119) for sneezing, 72% (120/166) for nasal discharge, 91% (185/204) for nasal obstruction, and 87% (177/204) for overall nasal symptoms. In particular, nasal obstruction disappeared completely in 50% (102/204) and improved remarkably in 22% (46/204), with a significantly higher efficacy rate compared to sneezing and nasal discharge ($p < .01$, histamine test). Concerning long-term results (more than 2 years after surgery), laser surgery was effective in 81% (26/32) for sneezing, 78% (32/41) for nasal discharge, and 76% (38/50) for nasal obstruction.

We conclude that laser surgery is an effective treatment for nasal allergy.

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SUPPLEMENT 181 — MAY 2000
Volume 109, Number 5, Part 2

TEMPORAL BONE STUDIES OF THE HUMAN PERIPHERAL VESTIBULAR SYSTEM

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2. NORMATIVE SCARPA'S GANGLION CELL DATA
3. AMINOGLYCOSIDE OTOTOXICITY
4. MENIERE'S DISEASE

ANNALS
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PREFACE

Systematic study of the microscopic anatomy and pathology of the ear goes back at least as far as Joseph Toynbee and Adam Politzer in the 19th century. Quantitative otopathology was born in 1921 with Stacy Guild's description of graphic reconstruction of the organ of Corti. John R. Lindsay, his student Harold F. Schuknecht, and Schuknecht's many students have developed modern otopathology to its present level. In the latter half of the 20th century, modern otopathology has sought to correlate structure and function in an effort to deepen our understanding of the normal and pathological ear. However, the story of modern otopathology has been the story of *cochlear* otopathology. A Medline search of the National Library of Medicine, depending on search terms, yields between 1,200 and 2,500 citations on histopathology of the ear. Only about 200 to 250 of these include information on the vestibular system. Fewer than 5 present data from quantitative studies of vestibular otopathology. A major impediment to quantitative vestibular otopathology has been the limitations imposed by the complex 3-dimensional anatomy of the vestibular labyrinth. Conventional histologic processing of temporal bones as described by Schuknecht and others is optimized for study of the cochlea. There is no single plane of sectioning that will provide equally advantageous exposure for all 5 vestibular end organs. However, there is a wealth of archival temporal bone histopathologic specimens and medical records contained in the various temporal bone collections in existence today.

We recently developed a new method for quantitative otopathological assessment of the vestibular system using archival temporal bones processed in the standard fashion for light microscopy (Merchant SN. A method for quantitative assessment of vestibular otopathology. Laryngoscope 1999;109:1560-9). The technique uses Nomarski differential interference contrast microscopy to enable unequivocal differentiation of hair cells from supporting cells and type I from type II hair cells in the vestibular end organs. We present 4 papers in this supplement. In the first, we applied the Nomarski optics technique to a series of 67 temporal bones from birth to age 100, thus creating a normative database of type I and type II hair cell counts within the 5 vestibular end organs. The second paper comprises a similar normal age series of vestibular (Scarpa's) ganglion cell counts. The next 2 papers apply the Nomarski optics technique to temporal bones from patients with aminoglycoside ototoxicity and Meniere's disease. The normative data of the first 2 papers provide a context in which to interpret results obtained in pathological ears such as those studied in the latter 2 papers. We believe the papers in this supplement demonstrate both the feasibility and merit of quantitative vestibular otopathology, a new branch of modern otopathology that promises to grow in coming years.

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TEMPORAL BONE STUDIES OF THE HUMAN PERIPHERAL VESTIBULAR SYSTEM

1. NORMATIVE VESTIBULAR HAIR CELL DATA

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Quantitative studies of the vestibular system with serially sectioned human temporal bones have been limited because of difficulty in distinguishing hair cells from supporting cells and type I from type II hair cells. In addition, there is only a limited amount of normative data available regarding vestibular hair cell counts in humans. In this study, archival temporal bone sections were examined by Nomarski (differential interference contrast) microscopy, which permitted visualization of the cuticular plate and stereociliary bundle so as to allow unambiguous identification of hair cells. The density of type I, type II, and total numbers of vestibular hair cells in each of the 5 sense organs was determined in a set of 67 normal temporal bones that ranged from birth through 100 years of age. The mean total densities at birth were 76 to 79 cells per 0.01 mm^2 in the cristae, 68 cells per 0.01 mm^2 in the utricle, and 61 cells per 0.01 mm^2 in the saccule. The ratio of type I to type II hair cells at birth was 2.4:1 in the cristae and 1.3:1 in the maculae. There was a highly significant age-related decline in all sense organs for total, type I, and type II hair cell densities that was best fit by a linear regression model. The cristae lost type I cells with advancing age at a significantly greater rate than the maculae, whereas age-related losses for type II cells occurred at the same rate for all 5 sense organs. Hair cell densities in the cristae were significantly higher at the periphery than at the center. There were no significant sex or interaural differences for any of the counts. Mathematical models were developed to calculate the mean and 95% prediction intervals for the total, type I, and type II hair cell densities in each sense organ on the basis of age. There was overall good agreement between the hair cell densities determined in this study and those reported by others using surface preparation techniques. Our data and related models will serve as a normative database that will be useful for comparison to counts made from subjects with known vestibular disorders.

KEY WORDS — temporal bone, vestibular hair cell.

INTRODUCTION

The traditional technique of light microscopic study of human temporal bones involves fixation, decalcification, celloidin embedding, serial sectioning at 20-µm thickness, and hematoxylin and eosin (H & E) staining of every 10th section.[1] The various temporal bone laboratories in the United States collectively contain more than 12,000 specimens that have been processed in this manner,[2,3] a large repository of tissue that has been extensively used for quantitative assessment of cochlear disorders. However, quantitative studies of the vestibular system have been limited, because it has been generally difficult to reliably differentiate hair cells from supporting cells, and type I hair cells from type II hair cells.[1] In addition, there is only a limited amount of normative data available regarding vestibular hair cells.

We have recently developed a method to overcome the above limitations and make a quantitative assessment of type I and type II vestibular hair cells in archival temporal bone sections.[4] This method involves the use of Nomarski (differential interference contrast) microscopy at high power, which enables one to visualize the cuticular plate and stereociliary bundle, and allows unambiguous identification of hair cells. Type I and type II hair cells can then be distinguished by their morphological characteristics. In the present study, we determined the density of type I, type II, and total numbers of vestibular hair cells in each of the 5 vestibular sense organs in a set of 67 normal temporal bones ranging from birth through 100 years of age. The counts were analyzed with respect to age, sex, and interaural differences. Mathematical models were then developed to calculate the mean and 95% prediction intervals for the total, type I, and type II counts in each sense organ. We also compared the densities determined in this study with those reported by investigators using surface preparation techniques. The results reported herein will serve as a normative database against which one can compare counts made in temporal bones from

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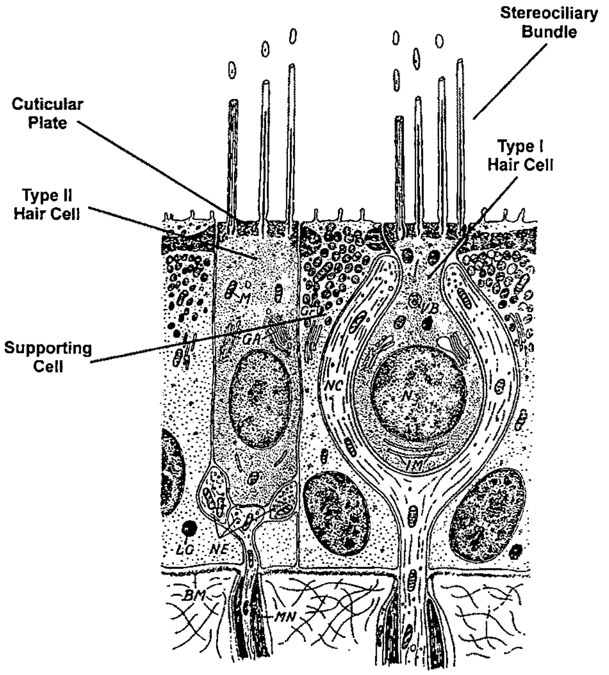

Fig 1. Schematic drawing of vestibular sensory epithelium. Type I hair cell is flask-shaped, is surrounded by nerve chalice of afferent fiber, and has spherical nucleus. Type II hair cell is cylindrical, does not have nerve chalice, and is innervated by many afferent and efferent nerve endings at its base. Both type I and type II hair cells have cuticular plate and stereociliary bundle. Supporting cells have neither stereociliary bundle nor cuticular plate and are not innervated. (Reproduced with permission.[5])

subjects with known vestibular disorders.

MATERIALS AND METHODS

Selection of Temporal Bones. The material for this study came from the temporal bone collection at the Massachusetts Eye and Ear Infirmary. These bones had been processed by the standard technique for study by light microscopy, including fixation, decalcification, celloidin embedding, serial sectioning in the axial (ie, horizontal) plane at 20-µm thickness, and H & E staining of every 10th section.[1] Vestibular hair cell counts were made in 67 normal temporal bones from 49 individuals. These temporal bones were grouped by age: 14 from neonates 0 to 28 days of age, 7 from infants 1 to 12 months of age, and 2 to 8 from each decade of life up to 100 years. All temporal bones had to meet 2 criteria: no symptoms or signs of inner ear disease except for presbycusis in the medical case history *and* no abnormality in the inner ear on light microscopy. For the purposes of this study, presbycusis was defined as bilateral, symmetric, slowly progressive sensorineural hearing loss that occurred after the age of 50 years and was documented audiometrically. All bones had to be well preserved, with minimal or mild postmortem autolysis, so that hair cell counts could be performed. Of the 67 bones, 37 (55%) were from men, and 37 (55%) were from the right side.

Method of Quantitative Assessment of Vestibular Hair Cells. The vestibular sensory epithelia are located on the maculae of the utricle and saccule and on the cristae of the 3 semicircular canals. The epithelia consist of hair cells and supporting cells. As originally described by Wersäll[5] and Engström et al,[6] there are 2 types of hair cells (Fig 1). Hair cells are characterized by a cuticular plate and a stereociliary bundle, neither of which is seen in supporting cells. Type I hair cells are flask-shaped, have a round bottom and a spherical nucleus, and are surrounded by a nerve chalice from an afferent branch of the vestibular nerve. Type II hair cells are cylindrical, with no nerve chalice surrounding the cell body, and they have a more cylindrical nucleus. The type II cells are innervated by bouton-type terminals from both afferent and efferent nerve endings.

We have developed a method that permits the reliable identification of type I and type II hair cells in the various vestibular sense organs on archival temporal bone sections prepared in the standard manner for conventional light microscopy.[4] This method involves using Nomarski (differential interference contrast) microscopy at high power (×1,250), which allows the visualization of the cuticular plate and stereociliary bundle so that hair cells can be identified unambiguously. Type I and type II cells are distinguished by their morphological characteristics. Figure 2 shows a photomicrograph of an archival temporal bone section examined by Nomarski microscopy that demonstrates the capability of distinguishing the various cell types. A prerequisite for this method is that the tissue must be well preserved, with minimal or mild postmortem autolysis.

In the standard procedure for preparing temporal bones for light microscopic study, the bones are sectioned in the horizontal (axial) plane, and every 10th section is stained with H & E. The H & E–stained sections that contain the vestibular sense organs are used to perform hair cell counts. In our method, counts are made of type I, type II, and total (type I + type II) numbers of hair cells in all portions of the sensory epithelium of each vestibular sense organ in which the plane of section is *perpendicular* to the surface of the sensory epithelium. (In the saccule, in which all of the 9 or 10 sections through the saccule are perpendicular, counts are performed on the 3 middle sections only.) The hair cell counts are expressed as density: number of cells per 0.01 mm^2 of surface area. These density counts are corrected for potential double-counting of cells split between 2 sections by means of the formula of Abercrombie.[7] Correc-

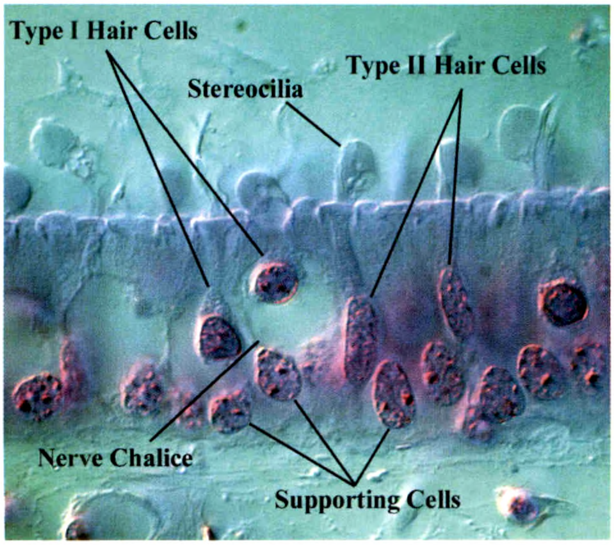

Fig 2. Photomicrograph with Nomarski microscopy taken of utricular macula of archival temporal bone (male, 54 years of age, 3 days after death). Round window membrane and stapes were removed 30 minutes after death, and inner ears were injected with Karnovsky's solution. Photomicrograph demonstrates cytologic features of hair cells and supporting cells. Outlines of individual hair cells can be followed from nucleus toward apical surface of cell, on which cuticular plate and stereociliary bundle can be identified. Type I hair cells are recognized by their flask shape, spherical nucleus, and nerve chalice surrounding cell body. Type II hair cells are identifiable by relatively cylindrical shape, oval nucleus, and absence of nerve chalice. Supporting cells have lightly stained nuclei with chromatin material distributed in clumps, and cells lack stereocilia and cuticular plates.

tion factors of 0.82 for type I hair cells and 0.87 for type II hair cells are used. Details of the technique have been described previously, and it has been shown to give reliable, valid, and repeatable counts.[4]

Statistical Analyses. The effects of age, sex, and interaural differences were determined by regression analyses. In many instances, the same individual contributed both ears to the sample population. There is a substantial correlation between counts in the 2 ears of the same individual, which can give erroneous p values if linear regression and other model analyses are performed in the standard fashion. (Errors can occur because in the standard approach using these models, it is assumed that the data points are independent of each other.) Therefore, in the present study, a linear regression model with a random subject effect[8] was used to account for some individuals who contributed 2 ears. As a result, the data from both ears of an individual could be included, thereby maximizing the number of specimens available for this study. The possibility of nonlinear relationships with age was also examined by including quadratic and cubic age effects.

RESULTS

The densities (cells per 0.01 mm^2) for total hair cell counts, type I counts, and type II counts are shown in Tables 1, 2, and 3, respectively. Each Table shows the mean density ± SD for each age group and each vestibular sense organ. Densities could be determined in all 67 bones for the 3 cristae and the utricular macula. Artifactual disruptions of the saccular macula precluded estimation of saccular cell densities in 5 bones, and hence, the saccular counts are based on 62 bones. Figures 3-7 show scatter plots of total, type I, and type II hair cell counts for each of the 5 vestibular sense organs. A regression line is drawn through each plot, indicating the best fit for the data.

Total Hair Cell Density in Terms of Age, Sex, and Interaural Correlation. The total hair cell densities in the 3 cristae were remarkably similar at birth, with a mean density of 76 to 79 cells per 0.01 mm^2. The individual values for the 3 cristae were not signifi-

TABLE 1. TOTAL HAIR CELL DENSITY COUNTS

Age Group	*N*	*Superior Crista*	*Lateral Crista*	*Posterior Crista*	*Utricular Macula*	*Saccular Macula*
0-1 mo	14	73.6 ± 9.3	77.2 ± 8.4	76.4 ± 6.9	67.8 ± 8.0	59.3 ± 7.9
1-12 mo	7	77.1 ± 10.3	77.1 ± 9.4	76.6 ± 8.3	66.6 ± 9.7	59.0 ± 10.9
1-10 y	4	75.5 ± 5.2	72.8 ± 3.0	75.3 ± 3.9	65.3 ± 2.8	65.8 ± 4.7
11-20 y	3	68.0 ± 12.0	77.7 ± 2.5	69.7 ± 8.0	66.0 ± 15.6	53.0 ± 0.0*
21-30 y	3	68.7 ± 9.3	71.3 ± 5.1	68.0 ± 11.4	71.0 ± 3.0	66.0 ± 5.7*
31-40 y	3	65.0 ± 6.0	68.3 ± 2.3	61.7 ± 10.7	65.0 ± 2.7	53.0 ± 2.0
41-50 y	2	57.0 ± 8.5	61.5 ± 2.1	65.0 ± 1.4	58.0 ± 5.7	55.0*
51-60 y	6	61.2 ± 6.3	63.3 ± 7.0	63.7 ± 4.7	57.2 ± 3.3	58.4 ± 8.8*
61-70 y	6	52.2 ± 11.6	54.8 ± 14.1	51.7 ± 14.0	56.2 ± 13.8	47.7 ± 8.5
71-80 y	6	41.5 ± 5.5	50.8 ± 7.8	41.5 ± 7.9	56.2 ± 9.5	45.3 ± 7.5
81-90 y	8	44.5 ± 11.9	42.9 ± 6.5	42.4 ± 9.9	51.0 ± 9.0	39.1 ± 6.2*
91-100 y	5	45.2 ± 8.6	46.0 ± 6.4	41.4 ± 11.0	62.2 ± 15.8	47.8 ± 16.1

Data are hair cells per 0.01 mm^2 (mean ± 1 SD).

*One temporal bone of group was not used for this measurement (ie, N was smaller by 1).

TABLE 2. TYPE I HAIR CELL DENSITY COUNTS

Age Group	*N*	*Superior Crista*	*Lateral Crista*	*Posterior Crista*	*Utricular Macula*	*Saccular Macula*
0-1 mo	14	51.1 ± 8.1	55.4 ± 8.8	54.8 ± 7.2	38.6 ± 3.3	34.1 ± 4.4
1-12 mo	7	54.7 ± 7.1	55.7 ± 6.0	54.1 ± 6.4	37.7 ± 7.5	35.0 ± 6.4
1-10 y	4	49.5 ± 2.4	52.3 ± 3.1	53.3 ± 1.5	33.3 ± 3.3	36.8 ± 5.7
11-20 y	3	45.0 ± 4.6	53.3 ± 3.1	49.0 ± 5.6	38.7 ± 5.8	34.5 ± 2.1*
21-30 y	3	44.0 ± 5.2	47.7 ± 5.7	42.3 ± 2.5	35.0 ± 4.4	33.5 ± 5.0*
31-40 y	3	43.3 ± 3.2	49.0 ± 7.2	42.3 ± 7.5	36.3 ± 3.2	32.7 ± 1.2
41-50 y	2	42.0 ± 2.8	46.5 ± 5.0	47.5 ± 0.7	35.5 ± 3.5	37.7*
51-60 y	6	41.0 ± 7.2	45.7 ± 7.2	42.8 ± 5.3	32.8 ± 6.4	32.4 ± 10.9*
61-70 y	6	35.3 ± 7.9	41.8 ± 13.1	34.7 ± 7.8	32.3 ± 4.6	30.2 ± 5.3
71-80 y	6	25.3 ± 3.3	34.3 ± 6.6	27.2 ± 6.1	29.3 ± 4.2	25.8 ± 4.6
81-90 y	8	27.5 ± 7.6	29.6 ± 6.6	26.4 ± 4.9	31.9 ± 4.3	25.7 ± 4.3*
91-100 y	5	29.6 ± 6.0	33.8 ± 4.8	27.4 ± 7.0	34.8 ± 3.9	28.4 ± 4.4

Data are hair cells per 0.01 mm^2 (mean ± 1 SD).

*One temporal bone of group was not used for this measurement (ie, N was smaller by 1).

cantly different from each other. After birth, the total counts for all 3 canals showed a strong negative correlation with age, best fit by a straight-line regression model. The age effect was highly significant (p < .0001). The slope of the regression line was the same for all 3 cristae, with no significant differences between the 3 canals (p > .05).

The mean total hair cell density at birth was 68 cells per 0.01 mm^2 for the utricle and 61 cells per 0.01 mm^2 for the saccule. These 2 numbers were significantly different from each other (p < .0001) and also significantly different from the mean counts at birth for the 3 cristae (p < .0001). After birth, the total counts for the utricle and saccule showed a strong negative correlation with age, which was also best fit by a straight-line regression model. The age effects were similar for the utricle and saccule, and the slopes of the 2 regression lines did not differ significantly from each other (p > .05).

The rate of cell loss with age was significantly greater for the cristae than for the maculae (p < .0001). In other words, the cristae lost cells at a greater rate than the maculae with advancing age. Statistical analyses revealed no significant difference at the .05 level between men and women or between right and left ears. These sex and interaural analyses controlled for differences in age.

Type I and Type II Hair Cell Densities in Terms of Age, Sex, and Interaural Correlation. The mean density of type I hair cells at birth was 52 to 56 cells per 0.01 mm^2 in the 3 cristae and 35 to 38 cells per 0.01 mm^2 in the maculae. After birth, there was a strong age-related decline in all sense organs (p < .0001) that was best fit by a linear regression model. The slope of the age-related decline was significantly steeper for the cristae than for the maculae (p < .0001). Thus, whereas each crista lost approximately 3 cells per 0.01 mm^2 per decade of life, each macula

TABLE 3. TYPE II HAIR CELL DENSITY COUNTS

Age Group	*N*	*Superior Crista*	*Lateral Crista*	*Posterior Crista*	*Utricular Macula*	*Saccular Macula*
0-1 mo	14	22.5 ± 8.1	21.7 ± 4.6	21.6 ± 5.6	29.1 ± 6.7	25.1 ± 6.2
1-12 mo	7	22.4 ± 4.2	23.3 ± 5.2	22.4 ± 3.2	28.9 ± 5.4	24.0 ± 6.8
1-10 y	4	25.8 ± 3.9	20.0 ± 2.9	22.3 ± 4.4	32.0 ± 3.5	29.0 ± 4.1
11-20 y	3	23.0 ± 9.6	24.3 ± 4.7	21.0 ± 6.6	27.3 ± 13.3	18.5 ± 2.1*
21-30 y	3	24.7 ± 6.7	23.7 ± 0.6	25.7 ± 9.0	36.0 ± 2.0	32.5 ± 0.7*
31-40 y	3	21.7 ± 3.2	19.3 ± 5.0	19.3 ± 3.2	28.7 ± 3.8	20.3 ± 2.3
41-50 y	2	15.0 ± 5.7	15.0 ± 2.8	17.5 ± 0.7	22.5 ± 2.1	17.2*
51-60 y	6	20.2 ± 4.1	17.7 ± 2.0	20.8 ± 3.3	24.3 ± 5.4	26.0 ± 8.3*
61-70 y	6	16.8 ± 8.1	13.0 ± 5.5	17.0 ± 9.5	23.8 ± 10.1	17.5 ± 5.7
71-80 y	6	16.2 ± 7.4	16.5 ± 5.2	14.3 ± 5.6	26.8 ± 6.7	19.5 ± 4.7
81-90 y	8	17.0 ± 6.0	13.3 ± 3.5	16.0 ± 6.3	19.1 ± 7.8	13.4 ± 5.8*
91-100 y	5	16.4 ± 4.7	12.2 ± 3.7	14.0 ± 4.9	27.4 ± 13.7	19.4 ± 12.3

Data are hair cells per 0.01 mm^2 (mean ± 1 SD).

*One temporal bone of group was not used for this measurement (ie, N was smaller by 1).

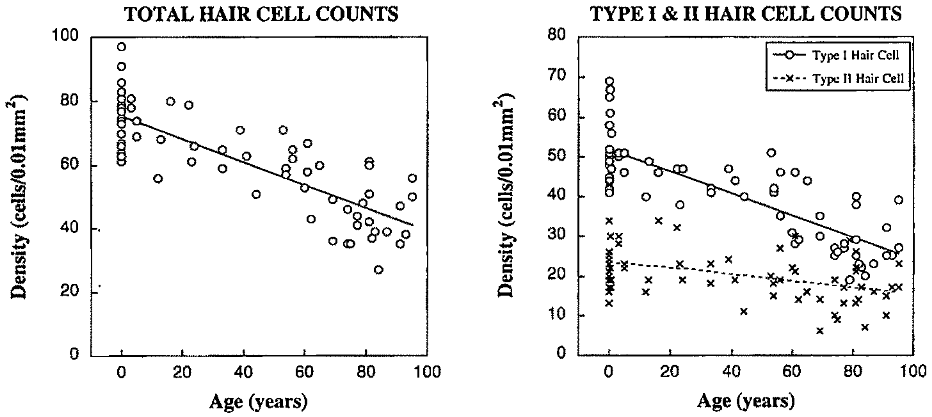

Fig 3. Normative hair cell data for crista of superior semicircular canal. Linearly fitted regression line is included in each plot (N = 67).

lost only approximately 1 cell per 0.01 mm². There were no statistically significant effects of sex or side for type I counts.

The mean density of type II hair cells at birth was 22 to 23 cells per 0.01 mm² in the 3 cristae, and 26 to 30 cells per 0.01 mm² in the maculae. After birth, there was a strong age-related decline in all sense organs ($p < .0002$) that was best fit by a linear regression model. However, unlike that of type I cells, the rate of age-related cell loss of type II cells did not differ between the cristae and the maculae ($p > .05$). Each crista and macula lost approximately 1 type II cell per 0.01 mm² per decade of life. There were no statistically significant effects of sex or side for type II counts.

Statistical Model Analyses. The best model fit for the total, type I, and type II hair cell counts was a linear equation for the cristae and for the maculae. The possibility of a squared, cubic, or quadratic relationship with age was considered, but these alternatives did not significantly improve the fit of the predictive equation as compared with the linear model. The equation used to predict the mean total, type I, or type II hair cell density (number of cells per 0.01 mm²) was: predicted mean density = intercept + (slope × age), where *intercept* is the predicted mean density at birth, *slope* is that of the regression line, and *age* is in years. Table 4 gives the values of the intercept and slope for each of the 5 sense organs used to calculate the total, type I, and type II mean predicted densities.

The regression model was also used to derive the 95% prediction intervals for a subject of a given age for total, type I, and type II hair cell densities for each of the individual sense organs. The general equation used to predict these 95% intervals was as follows: 95% prediction interval = predicted mean density $\pm$ $1.96 \times \sqrt{VP1 + VP2 + VP}$, where *predicted mean density* is calculated from the earlier equation, *VP1* (variance parameter 1) is the random variability between subjects, *VP2* (variance parameter 2) is the random variability within subjects (ie, right versus left ears), and *VP* (variance of prediction) = (variance of intercept) + (age² × variance of slope) + (2 × age × covariance of intercept and slope).

Table 5 lists the variance parameters, variances, and covariances for the individual sense organs for total, type I, and type II counts. Thus, the 95% prediction intervals can be determined for a subject of any given age and will be useful in future studies for comparing the hair cell counts measured from any given temporal bone with those of the normative database.

Comparison of Results to Surface Preparation

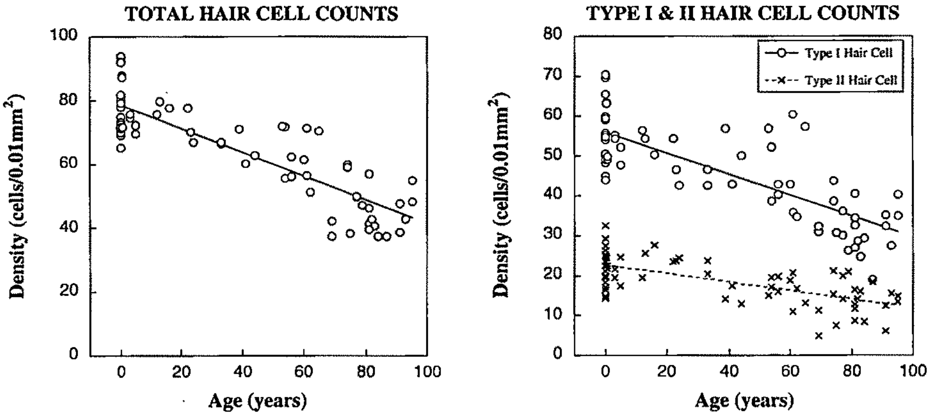

Fig 4. Normative hair cell data for crista of lateral semicircular canal. Linearly fitted regression line is included in each plot (N = 67).

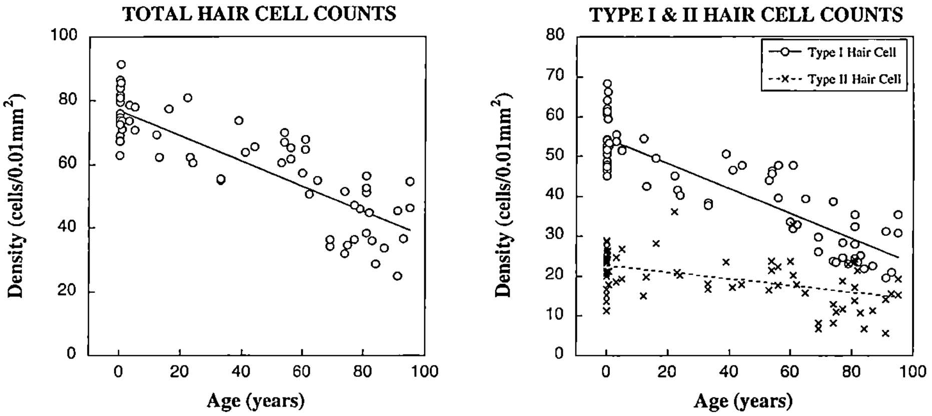

Fig 5. Normative hair cell data for crista of posterior semicircular canal. Linearly fitted regression line is included in each plot (N = 67).

Data and Other Temporal Bone Data. The hair cell densities measured in this study are compared with those reported by Rosenhall[9-11] in Fig 8. Rosenhall determined hair cell densities by sampling various parts of the sense organs in 58 temporal bones using a surface preparation technique. He reported the mean hair cell density for 3 age groups: 0 to 40 years, 40 to 70 years, and 70 to 90 years. The results were expressed separately for the peripheral versus the central regions of the cristae, and separately for the striolar versus the nonstriolar regions of the maculae. In Fig 8, the densities for all 3 cristae from our study were pooled, because they did not differ significantly from each other and because Rosenhall's data were also reported in a pooled fashion. It is evident that Rosenhall's mean densities for the 3 cristae and for the utricle fall within the 95% prediction intervals seen in this study. For the saccule, Rosenhall's densities are somewhat greater than those seen in this study, especially for ages greater than 40 years.

Figure 9 contains plots comparing the densities from the present study with those reported by Watanuki and Schuknecht.[12] Watanuki and Schuknecht's data were derived from total counts made by the surface preparation technique in 1 or 2 patients (42 to 53 years of age) for each sense organ. Watanuki and Schuknecht's data for each of the 3 cristae are within the 95% prediction intervals seen in this study, whereas their densities for the utricle and saccule are somewhat greater than the upper limit of the 95% prediction intervals seen in this study.

In general, there is agreement between the results of density counts determined by our technique on horizontally sectioned temporal bone material and the densities estimated by the surface preparation technique. Some of the densities in the surface preparation technique for the saccule and utricle were higher than those observed in this study. The reasons for such a discrepancy are not entirely clear. One possibility is simply normal variation within the population. Another possibility is differences in tissue preparation, because the fixatives and histologic processing techniques are quite different for the 2 methods. In the surface preparations, the cristae and maculae are no longer attached to adjacent structures of the membranous labyrinth, and therefore are potentially susceptible to slightly greater shrinkage (induced by fixation) than in the temporal bone serial section technique. Such shrinkage would tend to increase the hair cell densities in the surface preparations. Because the maculae have greater surface areas than the cristae and because they are relatively flat, the increase in density caused by shrinkage artifact may be relatively greater in the maculae. These small differences notwithstanding, the overall agreement between the 2 methods suggests that the calculation of densities by

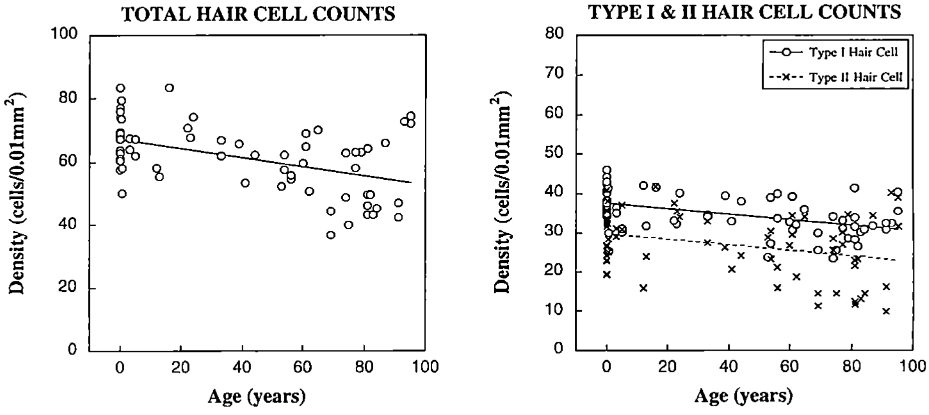

Fig 6. Normative hair cell data for macula of utricle. Linearly fitted regression line is included in each plot (N = 67).

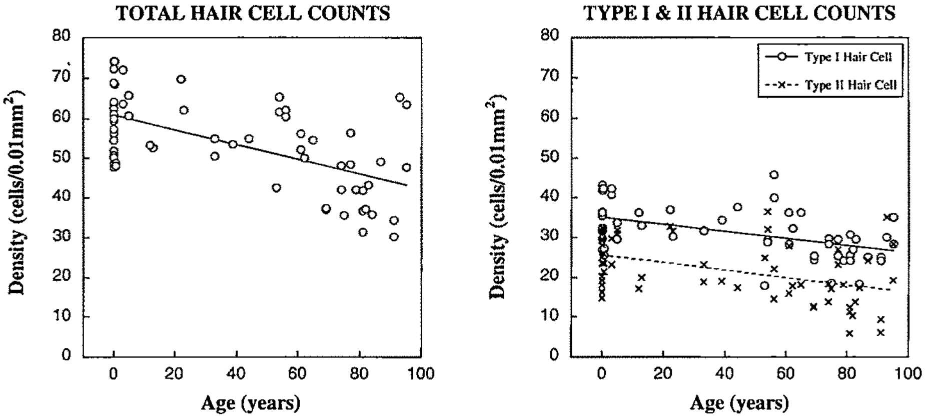

Fig 7. Normative hair cell data for macula of saccule. Linearly fitted regression line is included in each plot (N = 62).

the technique used in this study is valid.

One other study has attempted to quantitatively estimate the number of vestibular hair cells from archival human temporal bone material processed and sectioned as in this study. Richter[13] estimated hair cell densities in the various vestibular sense organs in 30 temporal bones from subjects who did not have vestibular disorders. Density was expressed as cells per 0.01 mm^2 of neuroepithelial surface area. Densities in the cristae and maculae were approximately 80 to 90 cells per 0.01 mm^2 in the first decade of life and decreased to approximately 40 to 60 cells per 0.01 mm^2 by the ninth decade. Richter's study differed from ours in that the cytologic scoring criteria for hair cells were subjective (Nomarski microscopy was not used), type I cells were not differentiated from type II cells, and counts were made on only a single section for each vestibular sensory end organ in a given temporal bone. Figure 10 shows a comparison of the densities in the present study and those reported by Richter. It is evident that Richter's results are well within the 95% prediction intervals seen in this study for most age groups for both cristae and maculae.

Hair Cell Densities at Peripheral Versus Central Regions of Cristae. The method used in the present study for determining hair cell densities in the cristae ignored the distinction between summit and periphery. Cell counts were made in all countable portions of each crista in order to sample the maximum possible surface area of each crista. However, it is certainly possible to restrict the counts only to the summit or the periphery, which would permit a comparison of hair cell densities between the 2 areas. Such an analysis was done in 9 normal temporal bones (from the total pool of 67 bones). Six subjects were neonates, 1 was a 2-month-old infant, 1 was 5 years of age, and 1 was 32 years of age. All stained sections from each crista were examined, and those portions in which the cut was perpendicular to the surface of the sensory epithelium were marked. Then, the marked area that most closely approximated the summit of the crista and the marked area that most closely represented the periphery were selected in each crista. Type I, type II, and total density counts were made on these selected sections in all 9 temporal bones. The results are shown in Table 6 and Fig 11.

Hair cell densities were significantly greater at the periphery than at the center ($p < 0.01$), in agreement with other human data from surface preparations.[9-12] The total hair cell densities for the center (about 70 cells per 0.01 mm^2) and periphery (about 87 cells per 0.01 mm^2) from this study are similar to Rosenhall's density estimates for the 0-to-40–year group for the center (about 67 cells per 0.01 mm^2) and periphery (about 81 cells per 0.01 mm^2), respectively. The density difference between the center and periphery is more marked for type I cells. As is evident from Fig 11, the type II cells were distributed more uniformly

TABLE 4. CALCULATION OF PREDICTED MEAN HAIR CELL DENSITIES

	Total Hair Cells		*Type I Hair Cells*		*Type II Hair Cells*	
Sense Organ	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*
Superior crista	75.5	–0.37	52.1	–0.29	23.4	–0.08
Lateral crista	79.0	–0.38	56.1	–0.27	22.8	–0.11
Posterior crista	77.6	–0.41	54.6	–0.32	22.7	–0.09
Utricle	68.2	–0.16	37.8	–0.08	30.2	–0.08
Saccule	61.2	–0.20	35.4	–0.10	25.8	–0.10

Densities (hair cells per 0.01 mm^2) were calculated with following equation: Predicted mean density = intercept + (slope × age), where *intercept* is predicted mean density at birth, *slope* is that of regression line, and *age* is in years.

TABLE 5. CALCULATION OF 95% PREDICTION INTERVALS FOR HAIR CELL DENSITIES

Sense Organ	*Hair Cell Count*	*Variance Parameter 1*	*Variance Parameter 2*	*Variance of Intercept*	*Variance of Slope*	*Covariance of Intercept and Slope*
Superior crista	Total	44.28	38.52	3.74	0.00126	−0.0528
	Type I	24.05	22.28	2.08	0.00070	−0.0293
	Type II	21.40	17.45	1.77	0.00059	−0.0249
Lateral crista	Total	39.43	22.87	2.93	0.00097	−0.0414
	Type I	33.12	23.00	2.59	0.00087	−0.0366
	Type II	8.96	9.98	0.83	0.00028	−0.0117
Posterior crista	Total	56.52	18.60	3.70	0.00122	−0.0522
	Type I	31.24	7.94	1.96	0.00064	−0.0276
	Type II	5.22	25.25	1.14	0.00040	−0.0161
Utricle	Total	81.22	9.92	4.70	0.00153	−0.0664
	Type I	13.63	9.02	1.05	0.00035	−0.0149
	Type II	49.86	11.89	3.10	0.00101	−0.0437
Saccule	Total	62.02	18.52	4.26	0.00137	−0.0588
	Type I	22.48	5.30	1.49	0.00048	−0.0206
	Type II	37.47	10.73	2.55	0.00082	−0.0353

Hair cell densities were measured in hair cells per 0.01 mm². See text for definitions of parameters.

between the summit and the periphery of the cristae.

DISCUSSION

Investigations into the anatomic and physiological structures of the human vestibular system and into the pathological and pathophysiological mechanisms of vestibular disorders would be facilitated by improvements in our ability to perform quantitative assessments of the vestibular sense organs. With traditional light microscopic serial sections, the correlation of functional abnormalities with cytologic changes has been less precise for the vestibular sense organs than for the cochlea. The main reason is that heretofore it has not been readily possible to distinguish hair cells from supporting cells or type I hair cells from type II hair cells in the vestibular sense organs with conventional light microscopy. The technique that we recently developed[4] and used in this study permits the reliable differentiation of these hair cell types in well-preserved specimens without need of any modifications to the technique of processing temporal bones for conventional light microscopy. This method has advantages compared with other techniques used to make vestibular hair cell counts, such as surface preparations. One is able to conduct simultaneous routine otopathological evaluations of the rest of the labyrinth and temporal bone. This is particularly valuable in the study of disorders that affect both vestibular and auditory functions. Another advantage is that the method does not preclude the application of newer and more innovative methods of temporal bone study such as electron microscopy, immunostaining, computer-aided reconstruction, and molecular biological methods with the polymerase

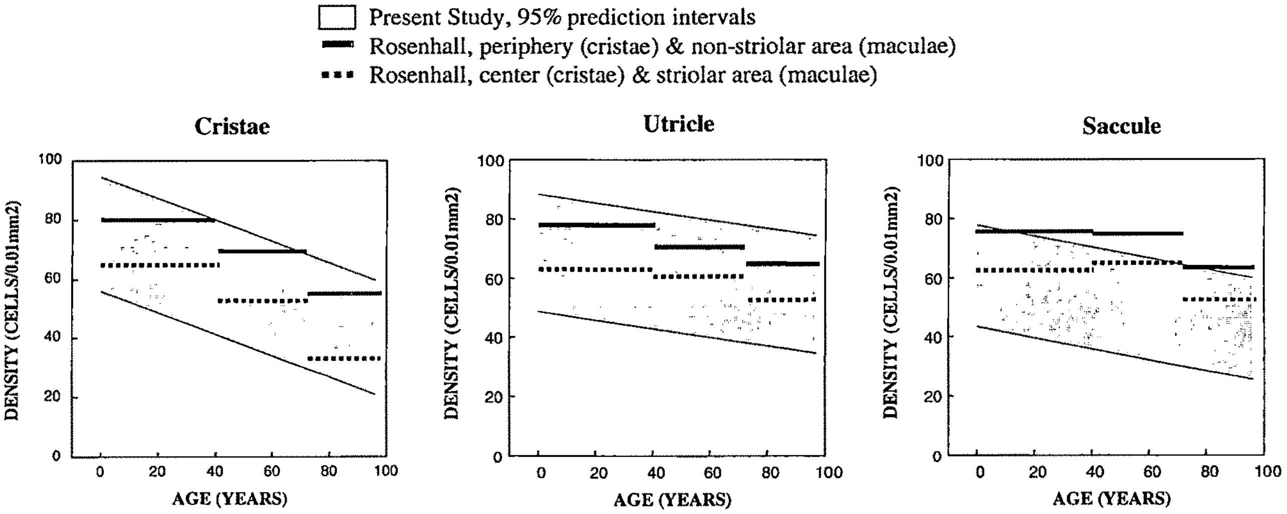

Fig 8. Comparison of total hair cell density counts found in present study to those reported by Rosenhall.[9-11]

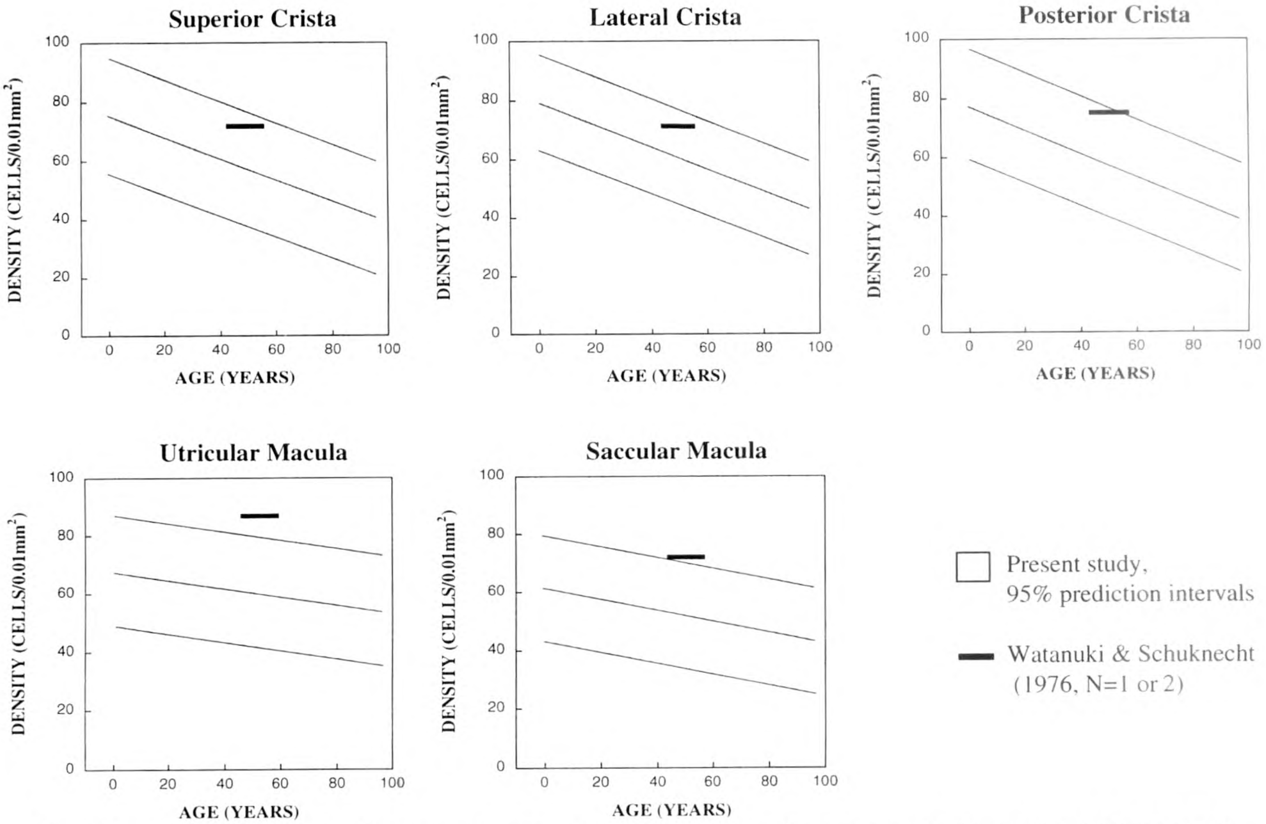

Fig 9. Comparison of total hair cell density counts found in present study to those reported by Watanuki and Schuknecht.[12]

chain reaction. It is also relatively inexpensive; adding the requisite Nomarski optics to a standard research light microscope costs $8,000 to $10,000. Because the method is applicable to archival temporal bones, research studies can be readily performed on the large number of archival specimens that currently exist in the various temporal bone laboratories.

There are also some limitations with the method that we have developed. It is applicable only to well-preserved specimens. Postmortem autolysis must be minimal-to-mild; otherwise, the cytoarchitecture is altered such that reliable differentiation of hair cells and supporting cells is not possible. The method is applicable only to areas of perpendicular sectioning. In conventional horizontal temporal bone sections, only parts of the cristae and maculae are sectioned perpendicular to the surface of the sensory epithelium. The mean percentage surface areas of each sense organ that are sectioned in a perpendicular plane, and

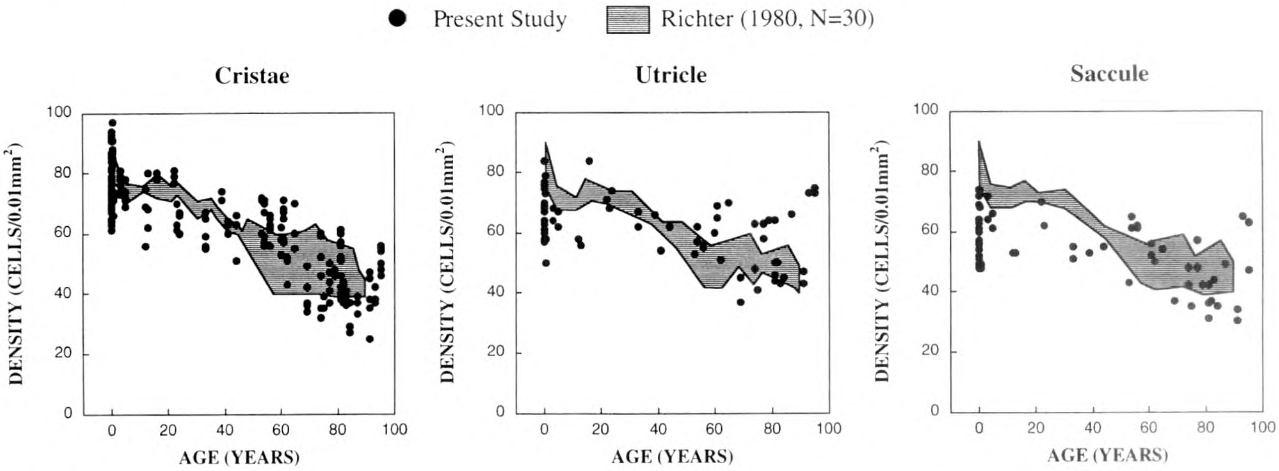

Fig 10. Comparison of total hair cell density counts found in present study to those reported by Richter.[13] Richter's results are shown as shaded area, and solid line represents outside envelope of his data points. Actual data points of present study are plotted as circles.

TABLE 6. HAIR CELL DENSITIES AT PERIPHERY VERSUS CENTER OF CRISTAE (N = 9)

Sense Organ		*Total Hair Cell Density*	*Type I Hair Cell Density*	*Type II Hair Cell Density*
Superior crista	Periphery	86.8 ± 12.0	59.9 ± 9.8	26.9 ± 4.2
	Center	72.3 ± 3.9	51.1 ± 2.6	21.0 ± 4.3
Lateral crista	Periphery	90.6 ± 8.2	66.2 ± 6.1	24.3 ± 3.7
	Center	67.6 ± 4.9	51.3 ± 4.0	16.2 ± 1.5
Posterior crista	Periphery	85.2 ± 6.2	62.4 ± 5.8	22.8 ± 2.7
	Center	70.6 ± 4.7	53.1 ± 3.5	17.4 ± 2.0

Data are hair cells per 0.01 mm^2 (mean ± 1 SEM).

therefore can be potentially assessed by this method, are 23% in the superior canal, 24% in the lateral canal, 28% in the posterior canal, 8% in the utricle, and 95% in the saccule.[4] With horizontal temporal bone sections, it is not possible to distinguish the striolar from the nonstriolar areas in the utricular and saccular maculae. It is known that the density of hair cells is lower in the striola[9,11,12]; however, the striola occupies only about 8% of the surface area of the otolith organs.[9,11] The density of hair cells is known to be uniform within the nonstriolar areas.[9,11,12] Hence, in developing this method of obtaining quantitative data of cell counts from the otolith organs, no distinctions were made regarding the anatomic subdivisions of the maculae.

This study was designed to generate a database of normative data for both type I and type II vestibular hair cells in each of the 5 sense organs. Such normative data enable us to analyze the effects of aging and other variables such as gender. Normative data are also essential to permit rational investigations of the effects of pathological conditions that affect the vestibular system. A special effort was made to include significant numbers of temporal bones from neonates and infants, which provide the best "control" populations, because they are least affected by aging or pathological disorders that might affect the inner ear. We also developed mathematical models to compute the mean densities and 95% prediction intervals for total, type I, and type II cells in each sense organ.

Many studies on the peripheral vestibular system conducted in the 1950s and 1960s suggested that the vestibular end organs were resistant to aging.[11] One of the reasons for this conclusion may have been that detailed evaluation of the vestibular end organs with quantitative techniques was difficult. Rosenhall's studies[9-11] were the first definitive investigations that clearly showed a loss of vestibular hair cells with advancing age. Our study not only confirms Rosenhall's conclusions, but also expands the normative data set and permits some interesting observations.

In the cristae, type I hair cells are lost at a more rapid rate with advancing age than are type II hair cells. For example, the ratio of type I to type II cells is 2.4:1 at birth, but becomes 2:1 by 80 years of age. Therefore, any evaluation of ratios of the 2 types of hair cells in the cristae must take age into consideration. On the other hand, the situation for the maculae seems to be different, as both cell types are lost at the same rate. The increased susceptibility of type I cells to degeneration with advancing age has also been noted by other investigators who performed electron microscopic evaluations in elderly animals and elderly humans.[14-16] The reason for a more rapid decline of type I cells in the cristae but not in the maculae is not clear. It has been suggested that type I cells are more susceptible to degeneration on phylogenetic grounds,[14,16] but this explanation must be reexamined in light of the findings of the present study. Perhaps the explanation may lie in the response

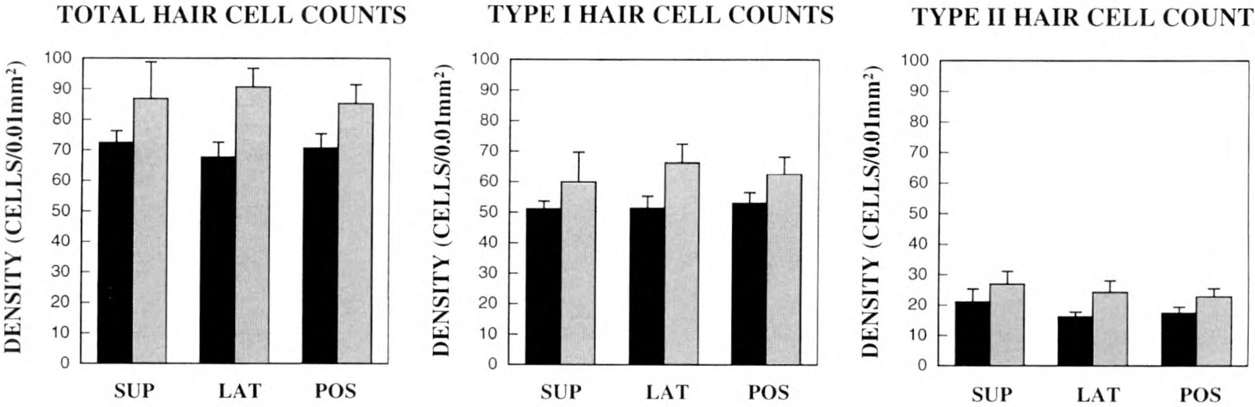

Fig 11. Comparison of hair cell densities at peripheral (gray bars) and central (black bars) regions of cristae (N = 9). Error bars — 1 standard error of mean; SUP — superior crista; LAT — lateral crista; POS — posterior crista.

dynamics and physiology of the cristae rather than in phylogeny.

Elderly individuals often experience vestibular symptoms, the so-called "disequilibrium of aging."[1] Much remains to be learned regarding the cause of such symptoms. The clear decline in numbers of both type I and type II hair cells with advancing age is likely to be one factor that leads to vestibular disturbances. It should be possible to design studies to compare the densities of hair cells from subjects with disequilibrium of aging with the normative data set generated in our present study to better understand the problem.

A number of investigations have examined the results of vestibular function tests in terms of advancing age.[17-21] Although results of some of the early studies were contradictory,[17-19] more recent studies[20,21] have shown an age-dependent deterioration in the vestibulo-ocular reflex. However, no study has addressed the morphological correlates of alterations in vestibular test results. Valuable information can be gained by quantifying the vestibular sense organs acquired from elderly subjects with well-documented vestibular test results.

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TEMPORAL BONE STUDIES OF THE HUMAN PERIPHERAL VESTIBULAR SYSTEM

2. NORMATIVE SCARPA'S GANGLION CELL DATA

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Scarpa's ganglion cell counts were performed in 106 serially sectioned, normal human temporal bones from 75 individuals. Of these 106 bones, 15 were from neonates less than 30 days old, 14 were from infants between the ages of 1 and 12 months, and the remainder were distributed throughout each decade of life, with sample sizes ranging from 4 to 10 per decade. All temporal bones had to meet 2 criteria: no symptoms or signs of inner ear disease except for presbycusis in the medical case history *and* no abnormality in the inner ear on light microscopy. The total ganglion cell counts declined significantly with age at an average rate of 57 cells per year. The age-related decline was significantly greater in the superior division than in the inferior division. There was also a significant sex effect, independent of age: for any age, the count in men averaged 1,526 cells higher than in women. There was no significant interaural difference. Mathematical models were developed to compute the mean and 95% prediction intervals for Scarpa's ganglion cell counts in terms of age and sex parameters. The counts and models will serve as a normative database against which to compare counts made in temporal bones from subjects with known vestibular disorders.

KEY WORDS — Scarpa's ganglion, temporal bone, vestibular ganglion.

INTRODUCTION

The vestibular or Scarpa's ganglion consists of neurons lying in 2 linearly arranged cell masses extending in a superior-inferior direction within the internal auditory canal.[1] The ganglion consists of a superior cell group and an inferior cell group, related to the 2 divisions of the vestibular nerve trunk. The superior division innervates the cristae of the superior and lateral semicircular canals, the macula of the utricle, and a small part of the saccular macula. The inferior division innervates the crista of the posterior semicircular canal and the major portion of the saccular macula. The ganglion cells are mainly bipolar in nature, although some are also multipolar.[2] Two cell types can be distinguished by light and electron microscopy: small cells with a mean diameter of 28 µm and large cells with a mean diameter of 40 µm.[3] The functional significance of these cell types is not known.

The purpose of this study was to determine the normal numbers of Scarpa's ganglion cells in humans at birth and to determine the effects of age, sex, and interaural differences. Particular attention was paid to including significant numbers of temporal bones from neonates and infants, which provide the best "control" populations, because they are least affected by aging or pathological disorders that might affect the inner ear. Mathematical models were developed to compute the mean and 95% prediction intervals for Scarpa's ganglion cell counts in terms of age and sex parameters. The counts and models will serve as a normative database against which to compare counts made in temporal bones from subjects with known vestibular disorders.

MATERIALS AND METHODS

Selection of Temporal Bones. The material for this study came from the temporal bone collection at the Massachusetts Eye and Ear Infirmary. These bones had been processed by the standard technique for study by light microscopy, including fixation, decalcification, celloidin embedding, serial sectioning in the axial (horizontal) plane at 20-µm thickness, and hematoxylin and eosin staining of every 10th section.[1] Scarpa's ganglion cell counts were performed in 106 normal specimens from 75 individuals. These temporal bones were grouped by age: 15 from neonates 1 to 28 days of age, 14 from infants 1 to 12

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TABLE 1. VALIDITY OF SCARPA'S GANGLION CELL COUNTS WITH ABERCROMBIE METHOD VERSUS DISECTOR METHOD

Specimen	*Abercrombie*	*Disector*
1	10	9
2	21	21
3	32	34
4	16	16
5	13	13
6	11	12
7	11	10
8	11	12
9	16	15
10	16	13

Pearson correlation, $\rho = 0.984$; $p < .0001$.
Counts are per 1 high-power field.

months of age, and 4 to 10 from each decade of life up to 100 years. Fifty-four bones (51%) were from men, and 53 bones (50%) were from right ears. All temporal bones had to meet 2 inclusion criteria: no symptoms or signs of inner ear disease except for presbycusis in the medical case history *and* no abnormality in the inner ear on light microscopy. For the purposes of this study, presbycusis was defined as bilateral, symmetric, slowly progressive sensorineural hearing loss occurring after the age of 50 years that was documented audiometrically.

Scarpa's Ganglion Cell Counts. Scarpa's ganglion cell counts were obtained by the technique outlined by Richter.[4] Each ganglion cell nucleus contains a single nucleolus. The nucleoli were counted in every stained section (ie, every 10th section) at a magnification of ×450. The section that showed the lowest number of ganglion cells was designated as the boundary between the superior and inferior divisions of the ganglion.

The raw ganglion cell counts were corrected for double counting of nucleoli split between 2 sections by the formula of Abercrombie[5]: $Hi = hi \times t/(t+d)$, where *Hi* is the corrected ganglion cell count, *hi* is the raw ganglion cell count, *t* is the section thickness (20 µm), and *d* is the diameter of the nucleolus.

The nucleolar diameter was measured in 100 ganglion cells, and the mean (±1 SD) diameter was 2.8 ± 0.48 µm. With Abercrombie's formula, a correction factor of 0.88 was determined. The number of counted cells multiplied by 0.88 and then multiplied by 10 (to account for unstained sections) gave the total count.

Statistical Analyses. The effects of age, sex, and side (interaural differences) were determined with regression analyses. In many instances, the same individual contributed both ears to the sample population. There is a substantial correlation between counts in the 2 ears of the same individual, which can give erroneous p values if linear regression and other model analyses are performed in the standard fashion. (Errors can occur because in the standard approach using these models, it is assumed that the data points are independent of one another.) Therefore, in the present study, a linear regression model with a random subject effect[6] was used to account for the fact that some individuals contributed 2 ears. As a result, the data from both ears of an individual could be included, thereby maximizing the available number of specimens for this study. The possibility of nonlinear relationships with age was also examined by including quadratic and cubic age effects. In separate regression analyses, we examined whether spiral ganglion cell counts or vestibular hair cell counts were independent predictors of Scarpa's ganglion cell counts, controlling for age and sex.

We also investigated whether the method of estimating Scarpa's ganglion cell counts using Abercrombie's correction[5] was "valid" (ie, whether the counts determined by this method were similar to

TABLE 2. SCARPA'S GANGLION CELL COUNTS

Age (y)	*N*	*Superior Division*	*Inferior Division*	*Total*
0-1 mo	15	13,213 ± 1,188	8,423 ± 1,158	21,636 ± 1,609
1-12 mo	14	13,166 ± 1,152	9,006 ± 1,338	22,172 ± 1,944
1-10	7	12,741 ± 1,590	9,349 ± 1,699	22,090 ± 1,711
11-20	8	12,927 ± 1,595	9,055 ± 601	21,982 ± 1,431
21-30	5	11,698 ± 771	7,897 ± 754	19,595 ± 1,118
31-40	4	13,919 ± 1,206	8,164 ± 582	22,083 ± 1,122
41-50	6	12,399 ± 1,004	7,722 ± 1,356	20,121 ± 2,254
51-60	10	10,882 ± 1,634	7,880 ± 874	18,763 ± 1,573
61-70	10	10,201 ± 1,151	7,661 ± 1,162	17,863 ± 1,886
71-80	10	10,167 ± 815	6,762 ± 963	16,930 ± 1,190
81-90	10	10,332 ± 936	8,199 ± 1,548	18,532 ± 1,755
91-100	7	10,136 ± 1,548	6,468 ± 898	16,604 ± 2,521

Data are mean ± 1 SD.

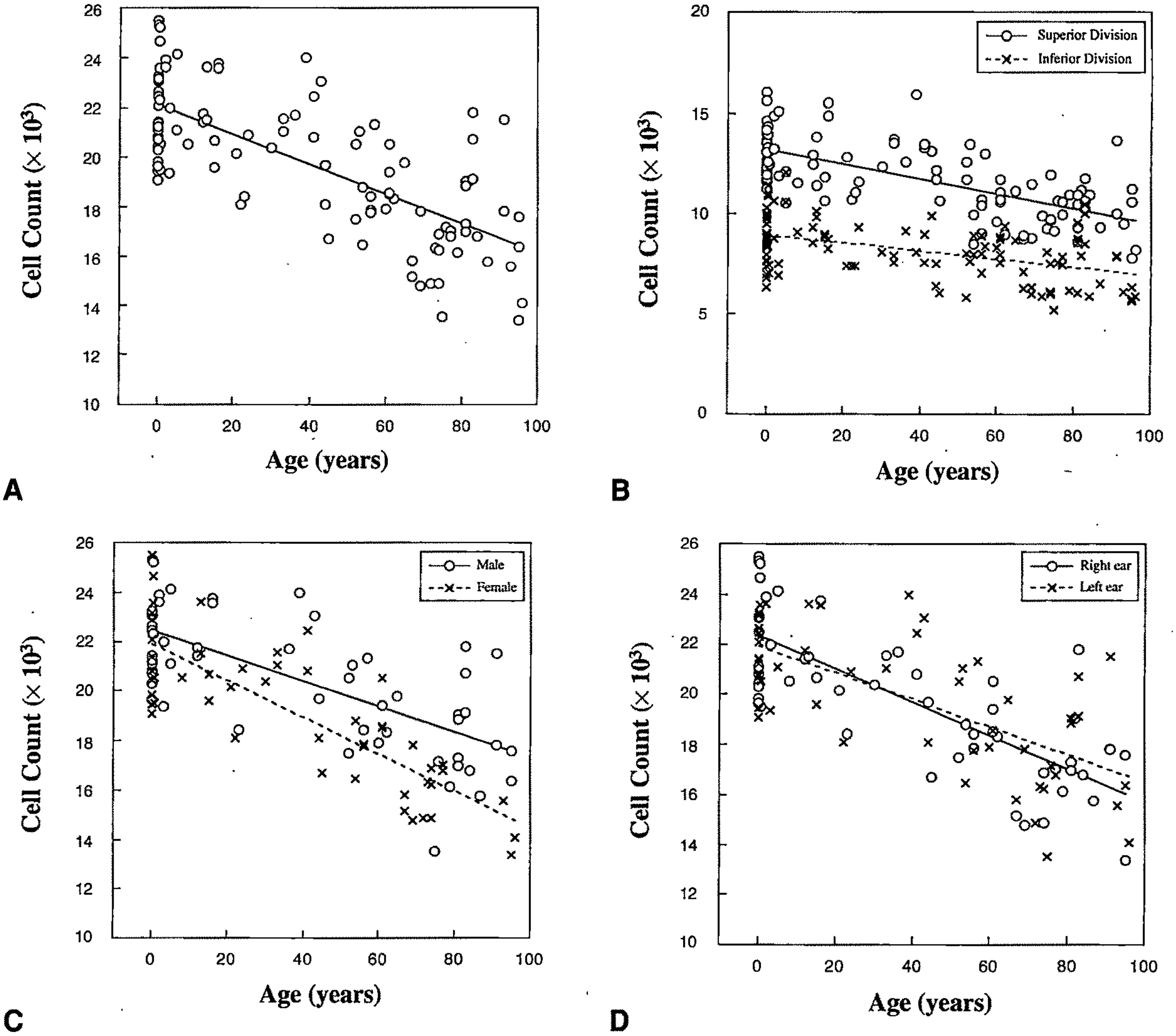

Fig 1. Scarpa's ganglion cell counts (N = 106). A) Total, normative data. B) Superior division versus inferior division. C) Male versus female. D) Right ear versus left ear.

the true count). Validity was determined by comparing counts made with Abercrombie's formula to counts made with an unbiased calibration technique based on the optical disector principle.[7] Counts were made by these 2 methods in sections from 10 different bones in 1 high-power field, and the results are shown in Table 1. There were no significant differences between the 2 methods (Pearson correlation, $\rho = 0.984$; $p < .0001$); thus, the Abercrombie method is indeed valid for counting ganglion cells. The optical disector method, although unbiased, is quite time-consuming and tedious. Further, the main purpose of Scarpa's ganglion cell counts is to compare counts between normal and various pathological states, rather than to determine absolute values. Because comparisons are performed between 2 sets of counts, any systematic bias in counting should cancel out of the calculation. For these reasons, we felt that it was appropriate to continue to use Abercrombie's technique for Scarpa's ganglion cell counts.

Spiral Ganglion Cell Counts. We also made estimates of the spiral ganglion cell count (cochlear neuronal count) in 94 of the 106 temporal bones. Spiral ganglion cell counts were obtained with the technique described by Schuknecht.[1] Briefly, each cell was counted by identifying its nucleolus. The cells were counted in every stained section (ie, every 10th section) at a magnification of ×450. Again, Abercrombie's formula[5] was used to correct for potential double-counting of nucleoli split between 2 sections. The mean (±1 SD) nucleolar diameter as measured in 100 spiral ganglion cells was 2.1 ± 0.26 µm. The correction factor was calculated to be 0.91. The number of counted cells multiplied by 0.91 and by 10 (to account for the unstained sections) gave the total estimated count.

RESULTS

Results of Scarpa's ganglion cell counts are expressed in terms of superior division, inferior divi-

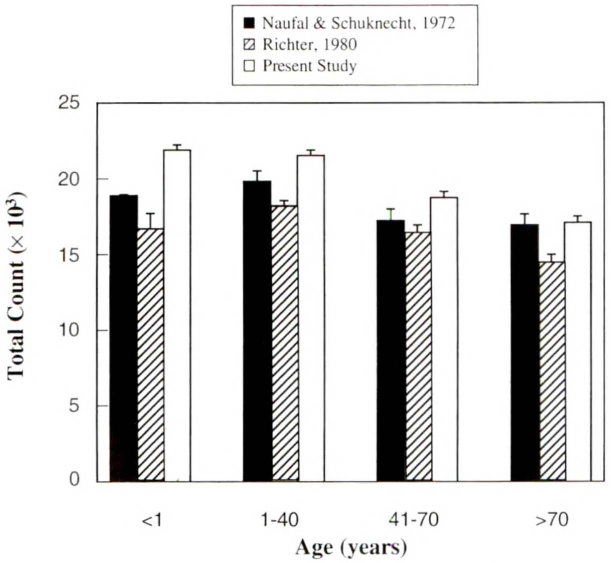

Fig 2. Comparative Scarpa's ganglion cell counts by methods of present study, Naufal and Schuknecht,[8] and Richter.[4] Error bars — 1 standard error of mean.

sion, and total counts. Table 2 shows the mean count ±1 SD for each age group. Figure 1 shows scatter plots of counts by age, sex, side, and division. A regression line is drawn through each plot that indicates the best fit of the data.

Age Correlation. Neonatal and infant temporal bones showed total Scarpa's ganglion cell counts of approximately 22,000. There was no significant difference between these 2 groups. After the age of 1 year, the total counts showed a strong negative correlation with age that was best fit by a straight-line regression model (Fig 1A,B). The age effect was highly significant ($p = .0001$). In a model that included counts from both the superior and inferior divisions, the superior division was found to lose an average of 17.6 (SE, 5.8) more cells per year than the inferior division ($p = .0025$). The superior division was predicted to lose 37.2 cells per year, and the inferior division was predicted to lose 19.6 cells per year. In this prediction, the model controlled for sex differences.

Sex Correlation. Statistical analysis revealed a significant sex effect, independent of age (Fig 1C). For any age, the count in men was, on average, 1,526.0 (SE, 376.7) cells higher than the count in women. The sex difference was highly significant ($p = .0003$). The rate of age-related decline was slightly greater in women than in men, but this difference was not statistically significant ($p = .08$). In an overall model predicting the total count and including age, sex, and a possible different age effect in men, the *difference* in counts between men and women was 19.6 (SE, 11.0) cells per year. That is, the predicted cell loss per year in men was 49.9, compared with 69.5 cells lost per year in women, but the trend for women to lose cells at a greater rate than men was not significant at the .05 level.

Interaural Correlation. Statistical analysis revealed no significant difference between right and left ears ($p > .05$; Fig 1D).

Model Analyses. The best model fit for the total count was a linear equation that took into consideration the effects of age and sex. The possibility of a quadratic or cubic relationship of age with total count was considered, and different age effects in men and women were also considered. None of these effects were significant at the .05 level.

The mathematical model for the predicted mean total count was as follows: Predicted mean value = intercept + (age × age effect) + (sex × female effect), where *intercept* is the predicted mean count at birth (22,809.6), *age* is in years, *age effect* = −56.81, *sex* = 0 for male and 1 for female, and *female effect* = −1,526.0.

Model analyses were also done to compute the 95% prediction intervals for the total count: 95% prediction intervals = predicted mean value ± 1.96 × $\sqrt{VP1 + VP2 + VP}$, where the *predicted mean value* is calculated from the first equation; *VP1* is variance parameter 1, the variance between subjects (1,589,434.98); *VP2* is variance parameter 2, the variance within subjects (right ear versus left ears; 1,403,311.07); and *VP* is the variance of prediction, which is calculated as follows: (variance of intercept) + (age^2 × variance of age effect) + (sex^2 × variance of female effect) + (2 × age × [covariance of age effect and intercept]) + (2 × age × sex × [covariance of age effect and female effect]) + (2 × sex ×

TABLE 3. PREVIOUS QUANTITATIVE STUDIES OF NUMBER OF VESTIBULAR NERVE FIBERS

Authors	*Date*	*Method*	*Age Group (y)*	*N*	*Mean*	*Range*
Rasmussen[9]	1940	Counts made central to Scarpa's ganglion	2-26	19	18,900	15,300-24,000
			44-60	18	18,000	14,200-22,900
Bergström[10]	1973	Counts made peripheral to Scarpa's ganglion	0-35	4	18,346	–
			49-53	2	16,700	–
			75-85	5	11,506	–
Fuji et al[11]	1990	Counts made at 3 sampling sites	43-93	12	17,727	13,996-20,760
Gleeson et al[12]	1996	Counts made peripheral to Scarpa's ganglion	54-82	17	19,023	15,468-21,073

[covariance of female effect and intercept]), where *variance of intercept* = 124,382.45, *variance of age effect* = 31.36, *variance of female effect* = 141,885.71, *covariance of age effect and intercept* = –1,322.11, *covariance of age effect and female effect* = 44.39, and *covariance of female effect and intercept* = –70,522.03.

Comparison Between Scarpa's and Spiral Ganglion Cell Counts. Total Scarpa's ganglion counts were *not* correlated with total spiral ganglion cell counts after adjusting for age and sex effects ($p > .05$).

Comparison Between Scarpa's Ganglion and Hair Cell Counts. Total Scarpa's ganglion counts were *not* correlated with vestibular hair cell counts (as determined in the previous study in this supplement, page 3) after adjusting for age and sex effects ($p > .05$).

DISCUSSION

We have shown that the neuronal population of Scarpa's ganglion differs between men and women and that the neuronal population declines in a linear fashion over the entire span of human life. Further, we have shown that the age-related loss of ganglion cells is greater in the superior division than in the inferior division of the ganglion. Findings in the present study will enable future investigations to correlate age-related vestibular symptoms with changes in vestibular hair cell and ganglion cell counts. It will be possible to determine whether there are vestibular equivalents of the sensory and neural types of presbycusis seen in the cochlea. Further, this normative database, in conjunction with normative hair cell data (this supplement, page 3), will be useful for investigating the effects of a variety of disorders that affect the vestibular system in a more precise and quantitative manner.

There have been 2 previous studies that used serially sectioned, hematoxylin and eosin–stained archival temporal bones to estimate the total number of Scarpa's ganglion cells in normal human specimens. Naufal and Schuknecht[8] counted the number of ganglion cells in 15 specimens from 9 patients ranging in age from 8 months to 84 years. The total number of ganglion cells in each stained section (every 10th section) was counted, and the number was multiplied by 10 to derive the total number of cells. Richter[4] did counts in a manner similar to that of Naufal and Schuknecht, but in addition, he used Abercrombie's correction formula[5] to account for double-counting of nucleoli split between 2 sections. Richter's correction factor was 0.83. He made cell counts from 54 human temporal bones with an age range from 9 weeks to 91 years.

As shown in Fig 2, the total ganglion cell counts in the present study are in general agreement with counts made by Naufal and Schuknecht[8] and by Richter.[4] In some age categories, the counts in the present study are higher. Some of the higher counts can perhaps be explained by the fact that the present study has a significantly larger number of infant and neonatal temporal bones, which have the highest counts. The studies of Naufal and Schuknecht and of Richter had very few temporal bones from neonates and infants. It is important to estimate the counts in these age groups, because they are the least affected by aging or pathological disorders that might affect the inner ear. Another possible reason for the somewhat higher counts in this study was that we used a correction factor of 0.88, which is somewhat higher than the 0.83 factor used by Richter.

Many authors have performed quantitative studies of the number of nerve fibers of the vestibular nerve, either peripheral or central to Scarpa's ganglion, from normal human temporal bone specimens.[9-12] These studies are summarized in Table 3, and their results are generally consistent with those of the present study and those of Richter[4] and Naufal and Schuknecht.[8] Because the vestibular nerve includes both afferent and efferent nerve fibers, nerve fiber counts are expected to be greater than ganglion cell counts. However, because there are only a small number of efferent fibers, it is reasonable to compare vestibular nerve fiber counts to Scarpa's ganglion cell counts. For example, the total number of efferent fibers in the cat vestibular nerve is 300 to 400, and there are only 400 to 500 efferent fibers in the squirrel monkey vestibular nerve.[13] Comparable human data are not available, but would probably be similar to the monkey data. Studies that use counts of nerve fibers provide accurate quantitative information regarding the vestibular nerve; however, they are time-consuming and tedious, and they also preclude examination of the remainder of the labyrinth. Nevertheless, they are useful and, by their similar results, support our method of estimating total Scarpa's ganglion cell counts by counting cells in every 10th section.

ACKNOWLEDGMENT — We thank Clarinda Northrop for providing some of the temporal bones in the neonatal and infant groups.

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TEMPORAL BONE STUDIES OF THE HUMAN PERIPHERAL VESTIBULAR SYSTEM

3. AMINOGLYCOSIDE OTOTOXICITY

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Quantitative assessments of vestibular hair cells and Scarpa's ganglion cells were performed on 17 temporal bones from 10 individuals who had well-documented clinical evidence of aminoglycoside ototoxicity (streptomycin, kanamycin, and neomycin). Assessment of vestibular hair cells was performed by Nomarski (differential interference contrast) microscopy. Hair cell counts were expressed as densities (number of cells per 0.01 mm^2 surface area of the sensory epithelium). The results were compared with age-matched normal data. Streptomycin caused a significant loss of both type I and type II hair cells in all 5 vestibular sense organs. In comparing the ototoxic effect on type I versus type II hair cells, there was greater type I hair cell loss for all 3 cristae, but not for the maculae. The vestibular ototoxic effects of kanamycin appeared to be similar to those of streptomycin, but the small sample size precluded definitive conclusions from being made. Neomycin did not cause loss of vestibular hair cells. Within the limits of this study (maximum postototoxicity survival time of 12 months), there was no significant loss of Scarpa's ganglion cells for any of the 3 drugs. The findings have implications in several clinical areas, including the correlation of vestibular test results to pathological findings, the rehabilitation of patients with vestibular ototoxicity, the use of aminoglycosides to treat Meniere's disease, and the development of a vestibular prosthesis.

KEY WORDS — aminoglycosides, ototoxicity, Scarpa's ganglion, temporal bone, vestibular hair cells.

INTRODUCTION

The vestibular and cochlear ototoxic effects of aminoglycosides in humans and animals are well known and well documented.[1,2] The evaluation of temporal bone specimens from patients who have had ototoxic drug effects is of fundamental importance for a variety of reasons.[2] Human specimens offer the most direct means of performing clinicopathologic correlations. They also allow for comparison of the results of animal studies to the human situation. Finally, human studies offer a histopathologic foundation for developing rational therapies. For example, certain aminoglycosides, such as streptomycin and gentamicin, are used clinically to achieve selective chemical ablation of the vestibular system for treatment of Meniere's disease.

A number of human temporal bone studies have looked at the auditory effects of aminoglycosides.[1] In contrast, few studies have examined the vestibular side effects with temporal bone histopathology. Case reports with qualitative evaluations of vestibular ototoxicity have been published,[1-3] but quantitative evaluations have not been performed with human materials. Streptomycin is known to have a greater toxic effect on the vestibular system than on the cochlea. Animal experiments performed on different species have shown that vestibular lesions occur primarily in the cristae and that there is little or no damage to the maculae.[4-6] These same studies have shown that the loss of hair cells is most severe in the central parts of the cristae and that the type I hair cells are affected in greater numbers than the type II cells. Only a few comparable human studies have been performed. Two case reports of streptomycin ototoxicity have been published[1,2]; qualitative assessments of the vestibular end organs suggested that the cristae showed loss of hair cells with little loss in the maculae and that the central parts of the cristae were more affected than the periphery. An animal study by Lindeman[6] showed that in guinea pigs, kanamycin caused damage to the type I hair cells on the central parts of the cristae and in the striola of the utricle with minimal damage to the saccular macula. Type II cells were shown to be less susceptible than type I cells. Toyoda et al[7] found a delayed effect of kanamycin toxicity in the guinea pig vestibular system. In humans, qualitative assessments of 2 cases of kanamycin ototox-

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TABLE 1. CLINICAL DATA FOR CASES OF AMINOGLYCOSIDE OTOTOXICITY

Drug	Age (y)	Sex	Survival After Ototoxicity (mo)	Total Dose (g)	Symptoms: Hearing Loss	Symptoms: Disequilibrium	Dizzy at Death	Caloric Test
Streptomycin	76	M	4	15	No	Yes	?	Reduced, right
	53	M	72	10	No	Yes	Yes	No response, both
	55	M	6	?	No	Yes	Yes	
	35	F	12	?	Left	Yes	Yes	
Kanamycin	27	F	2	3	Both	No	?	
	19	F	2	16	Both	?	?	
	50	F	3	12	Both	?	?	
Neomycin	87	F	6	22	Both	?	?	
	54	F	18	?	Both	?	?	
	69	M	60	?	Both	?	?	

icity with hearing loss suggested that the vestibular sense organs were normal.[1,2] Animal studies have shown an auditory toxic effect of neomycin, whereas vestibular dysfunction has been characterized as less severe.[1] In humans, the vestibular sense organs were judged to be normal in 3 cases of neomycin ototoxicity.[2]

The goal of this study was to perform a quantitative assessment of hair cells and Scarpa's ganglion cells in temporal bones from patients who had aminoglycoside ototoxicity. We have previously developed a reliable and valid method of making these assessments[8] and have also gathered normative data regarding both hair cells and ganglion cells (this supplement, pages 3 and 14).

MATERIALS AND METHODS

Selection of Temporal Bones. The material for this study came from the temporal bone collection at the Massachusetts Eye and Ear Infirmary. These bones had been processed by the standard technique for study by light microscopy, which includes fixation, decalcification, celloidin embedding, serial sectioning in the axial plane at 20-μm thickness, and hematoxylin and eosin staining of every 10th section.[1] The temporal bone collection was examined to select patients who had clinical evidence of aminoglycoside ototoxicity. Clinical evidence was defined as the occurrence of documented sensorineural hearing loss, vestibular symptoms attributed *directly* to the administration of an aminoglycoside antibiotic, or both. Furthermore, cases with evidence of concurrent or additional ear disease that could have caused hearing loss or vestibular symptoms that could have confounded the ototoxic effect of the administered aminoglycoside were excluded.

By these criteria, 10 cases were identified and included in the study. An additional 7 cases of aminoglycoside administration and possible ototoxicity were excluded because of a lack of firm clinical evidence of hearing loss or vestibular symptoms or because of additional ear disease. The 10 included cases consisted of 4 patients with streptomycin ototoxicity, 3 with kanamycin ototoxicity, and 3 with neomycin toxicity. There were no cases with ototoxicity caused by gentamicin or other aminoglycosides.

Quantitative Assessment of Vestibular Hair Cells and Scarpa's Ganglion Cells. Counts of type I, type II, and total (type I + type II) vestibular hair cells were performed with a method we developed and described previously.[8] The hair cell counts are expressed as density, ie, the number of cells per 0.01 mm^2 of surface area of the sensory epithelium. From the 10 patients, there were a total of 17 temporal bones and 85 individual vestibular sense organs. The postmortem autolytic changes were too advanced to permit reliable counting of hair cells in 33 of the 85 sense organs. The vestibular nerve was present in 11 of the 17 bones, and Scarpa's ganglion cell counts (this supplement, page 14) were made in these 11 specimens. The measured hair cell densities and ganglion cell counts were then compared with age-matched control normative data (this supplement, pages 3 and 14).

Statistical Analyses. The effects of the drugs on the various hair cell densities and Scarpa's ganglion cell counts were analyzed by means of a linear regression model. The model adjusted for the effects of age and sex (as determined from normative data gathered in the previous 2 papers in this supplement). The model also included a random subject effect[9] to account for the fact that some individuals contributed 2 ears. A p value of .01 (not .05) was used to indicate statistical significance in the present study, because of the large number of associations that were tested.

RESULTS

Clinical Data. A summary of the clinical data of

TABLE 2. HAIR CELL DENSITIES IN VESTIBULAR SENSE ORGANS AND SCARPA'S GANGLION CELL COUNTS

Drug	*Age (y)*	*Sex*	*Side*	*Superior Crista*		*Lateral Crista*		*Posterior Crista*		*Utricle*		*Saccule*		*Scarpa's Ganglion*
				Type I	*Type II*	*Type I*	*Type II*	*Type I*	*Type II*	*Type I*	*Type II*	*Type I*	*Type II*	
Streptomycin	76	M	R	26	8	20	9	22	7			20	11	17,354
			L	32	5	32	8	28	8			24	9	
	53	M	R	4	3	4	3	6	4	18	8			
			L	4	2	6	4	4	5	20	11	14	7	
	55	M	R			12	8	15	8	17	8	17	11	18,207
			L	12	11	16	8	12	8			20	13	
	35	F	R	18	4	15	6	14	5	35	15			15,444
			L	12	4	15	4	15	8	33	16			16,104
Kanamycin	27	F	R									30	11	14,687
			L									30	9	13,834
	19	F	R											18,674
			L	9	5	10	5	12	6					15,066
	50	F	R			24	10	23	10	24	18			19,061
Neomycin	87	F	R	31	7	31	10	2	9	21	15			13,131
			L	25	13	29	12	25	8	29	16			13,778
	54	F	R							33	15	23	17	
	69	M	R							35	14			

Density data are hair cells per 0.01 mm^2.

the 10 cases examined is shown in Table 1. There were 3 groups of patients.

The group with streptomycin ototoxicity comprised 4 patients, 35 to 76 years of age. The postototoxicity survival time ranged from 4 to 72 months. All 4 patients had vestibular symptoms caused by the antibiotic. Only 1 of the 4 patients had associated hearing loss; the other 3 did not complain of hearing loss and did not have a drop in hearing levels. Bithermal caloric testing was performed in 2 patients: there was paresis in the right ear of 1 patient and an absent caloric response in both ears of the second patient.

Three patients had kanamycin ototoxicity; their ages ranged from 19 to 50 years. All 3 patients had bilateral sensorineural hearing loss caused by the antibiotic. One patient did not have vestibular symptoms, and the status of vestibular symptoms was unknown in the other 2. Vestibular testing was not done in any patient.

The 3 patients with neomycin ototoxicity were 54 to 87 years of age. All 3 patients had bilateral sensorineural hearing loss caused by neomycin. The status of vestibular symptoms was not known in any patient.

Hair Cell and Scarpa's Ganglion Cell Data. The raw data for the various hair cell densities and Scarpa's ganglion cell counts are shown in Table 2. Blank areas represent those sense organs from which data could not be obtained because of advanced autolysis or lack of tissue (eg, avulsion of the vestibular nerve from the internal auditory canal). The results for the total hair cell density counts are shown in graphic form in Fig 1. In this Figure, the normative counts from all 3 cristae were combined into 1 plot because there was no difference in total hair cell counts between the 3 cristae (this supplement, page 3). The normative data plots that are shown represent the 95% prediction intervals for the various sense organs.

Table 3 shows the results of linear regression model analyses of the effects of the 3 drugs on various hair cell and Scarpa's ganglion cell counts. Streptomycin caused a significant loss ($p < .01$) of total, type I, and type II hair cell densities in all 5 vestibular sense organs when compared with age-matched normative data. In comparing the ototoxic effect on type I hair cells versus type II hair cells, there was significantly greater type I hair cell loss for the cristae, whereas the type I and II losses were the same in the 2 maculae. Scarpa's ganglion cell counts were no different from those of normal age- and sex-matched control specimens. It is to be noted that the longest survival time after ototoxicity was only 12 months. (The patient with 72 months' survival after ototoxicity had avulsion of the vestibular nerve out of the internal auditory canal.) In 2 patients with streptomycin toxicity, caloric testing had been done, and the results are shown in Fig 2. In the case with no response to warm and cold stimulation bilaterally, the percentage of total hair cell loss (compared with mean normal-for-age) in the lateral semicircular canal cristae was greater than 80% in both ears. In the other

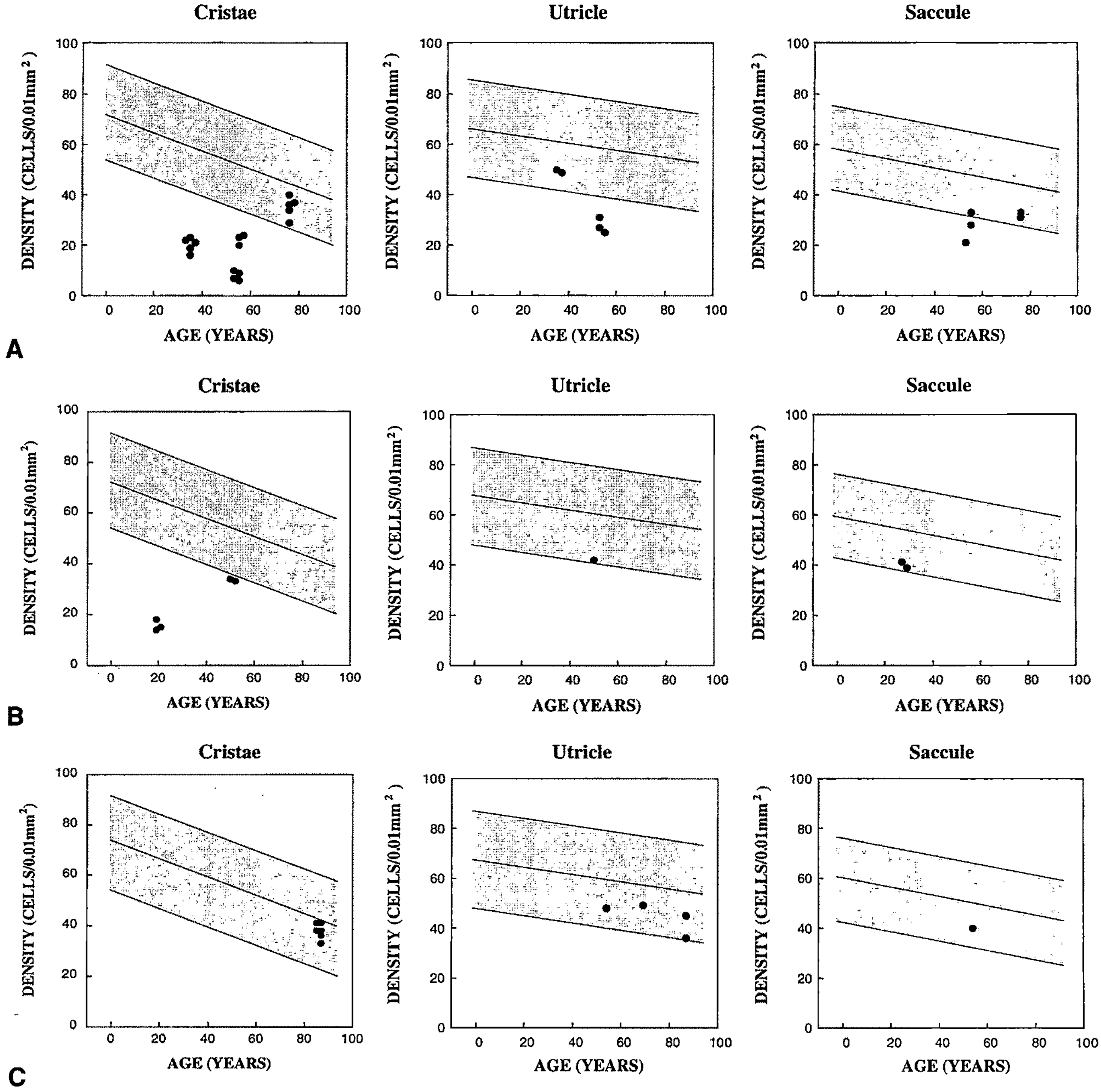

Fig 1. Comparison of total hair cell density counts between A) streptomycin and normative data, B) kanamycin and normative data, and C) neomycin and normative data. Shaded areas in gray represent 95% prediction intervals for normative data. Black circles represent pathological data (streptomycin, kanamycin, neomycin).

patient, who had a reduced right caloric response, the lateral canal crista showed a loss of 39% compared with the mean normal. The left ear of this latter patient had a normal caloric response, and there was a loss of 21% of hair cells within the lateral crista.

Kanamycin caused a significant loss ($p < .01$) of total, type I, and type II hair cells in all 3 cristae, and the ototoxic effect was greater on type I as opposed to type II cells. Kanamycin did not have any significant effects on hair cells in the 2 maculae, and Scarpa's ganglion cell counts were not different from normative data. Neomycin did not result in significant hair cell loss in any end organ, and Scarpa's ganglion cells were preserved after neomycin administration.

DISCUSSION

The analysis of pathological alterations as a result of aminoglycoside ototoxicity in this set of temporal bones has limitations, primarily because of the small numbers of bones examined (especially in the kanamycin and neomycin groups) and the relative paucity of vestibular test data. Nevertheless, the data allow for some interesting observations.

The data show that streptomycin appears to have

TABLE 3. RESULTS OF LINEAR REGRESSION MODEL ANALYSES SHOWING EFFECTS OF OTOTOXIC DRUGS ON HAIR CELLS AND SCARPA'S GANGLION CELLS

Vestibular Sense Organ	*Streptomycin*	*Kanamycin*	*Neomycin*
Superior crista			
Total hair cell counts vs normative data	.0001*	.0001*	.51
Type I hair cell counts vs normative data	.0001*	.0001*	.94
Type II hair cell counts vs normative data	.0001*	.0070*	.22
Type I vs type II hair cell counts	.018	.013	.30
Lateral crista			
Total hair cell counts vs normative data	.0001*	.0001*	.48
Type I hair cell counts vs normative data	.0001*	.0001*	.64
Type II hair cell counts vs normative data	.0001*	.006*	.51
Type I vs type II hair cell counts	.0001*	.001*	.83
Posterior crista			
Total hair cell counts vs normative data	.0001*	.0001*	.37
Type I hair cell counts vs normative data	.0001*	.0001*	.83
Type II hair cell counts vs normative data	.0001*	.0035*	.11
Type I vs type II hair cell counts	.0001*	.006*	.35
Utricle			
Total hair cell counts vs normative data	.0001*	.049	.041
Type I hair cell counts vs normative data	.0005*	.049	.53
Type II hair cell counts vs normative data	.0007*	.25	.027
Type I vs type II hair cell counts	.137	.78	.095
Saccule			
Total hair cell counts vs normative data	.0002*	.06	.23
Type I hair cell counts vs normative data	.0067*	.70	.29
Type II hair cell counts vs normative data	.0045*	.041	.61
Type I vs type II hair cell counts	.71	.051	.60
Scarpa's ganglion cell counts vs normative data	.070	.022	.15

Data are p values; * — $p < .01$.

a significant ototoxic effect on both the cristae and the maculae, a finding that is somewhat in contrast to what has been reported in the animal literature (wherein the cristae have been noted to be vulnerable and not the maculae). The greater toxic effect of streptomycin on type I hair cells as opposed to type II hair cells is consistent with findings in the animal literature.

For kanamycin ototoxicity, animal data have suggested a greater susceptibility for hair cells in the cristae than for those in the maculae, and a greater susceptibility for type I hair cell loss as opposed to type II. The human studies to date have suggested that the vestibular sense organs were not affected. In contrast, the results of this study suggest that the human vestibular system may be susceptible to kanamycin ototoxicity. The hair cell losses in the cristae from kanamycin were of a comparable magnitude to those sustained from streptomycin toxicity; however, because of the small sample size, caution must be exercised in drawing definitive conclusions.

For neomycin, the data suggest that there is little hair cell ototoxic effect in the vestibular sense organs; this finding is consistent with findings from previous reports in the literature on animals and humans.

It is also evident from the data that clinical symptoms of vestibular dysfunction do not require total loss of hair cells. For example, all patients with streptomycin ototoxicity were dizzy, and yet substantial numbers of hair cells were present in the maculae and cristae of these patients. All 3 ears with a reduced or absent caloric response had at least a 39% loss of hair cells within the lateral semicircular canal. The 1 ear with a normal caloric response had a 21% loss. This suggests that a reduction of 20% to 40% of hair cells may be necessary to produce caloric paresis. Obviously, examination of additional temporal bones with associated vestibular test data is needed to determine the minimum amount of hair cell loss necessary to give a reduced caloric response and to produce symptoms of disequilibrium. The ability to perform such clinicopathologic correlations has the potential to significantly enhance our understanding of caloric test results (and of vestibular function tests).

It would have been interesting to know the status of clinical symptoms for all the patients in this study

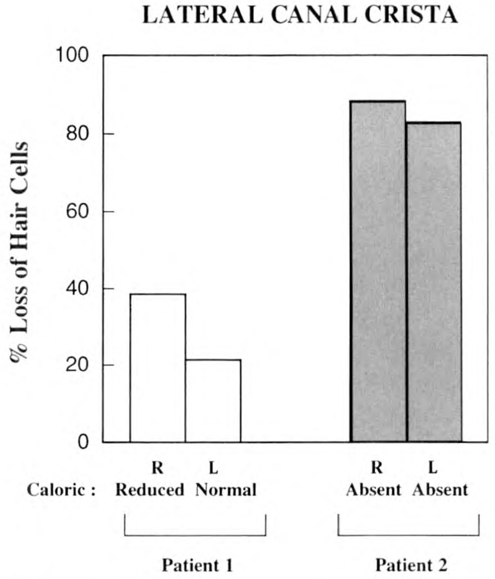

Fig 2. Percentage loss of hair cells in lateral canal (compared with mean, normal, age-matched control data) in 2 patients with streptomycin ototoxicity who had caloric testing.

near the time of their death. Particularly, it would be valuable to know whether they had compensated for the ototoxic insult to their peripheral vestibular system. Such information could then be correlated with the histologic findings. Perhaps there are differences in the degree of hair cell loss or ganglion cell loss in those patients who do not compensate for ototoxicity versus those who do. Such insight might allow refinement of the rehabilitative measures that are used to help people with ototoxicity.

The data also show that Scarpa's ganglion cells were relatively unaffected despite substantial hair cell loss. The longest postototoxic survival time was 12 months. (The 3 subjects with survival times greater than 12 months had avulsion of the vestibular nerves that precluded assessment of Scarpa's ganglion.) Within the time frame of this study, there was no evidence of significant retrograde neuronal degeneration from the periphery to Scarpa's ganglion. Obviously, examination of additional temporal bones with longer postototoxic survival times will be necessary to further investigate the long-term survival of Scarpa's ganglion cells. Such data have important implications for the development of a vestibular implant (analogous to the cochlear implant) designed to provide electrical stimulation of the vestibular periphery for patients with chronic disequilibrium and oscillopsia from aminoglycoside ototoxicity who have failed to respond to traditional vestibular rehabilitative measures.[10] If the peripheral processes and the vestibular ganglion cells remain generally intact despite hair cell loss, then a vestibular implant could theoretically be placed in the periphery such that differential stimulation of the individual canals and otolith organs would be possible.

Topical and systemic applications of streptomycin and gentamicin have been used to treat Meniere's disease. Ideally, the treatment aims to relieve vertigo while preserving hearing. Although the mechanism(s) of the therapeutic effect of these drugs is unknown, it is believed that ablation of vestibular hair cells may play a primary role. The streptomycin data from the present study show a clear ototoxic effect of the drug (when given systemically) on both the cristae and the maculae. The data also show that some surviving hair cells do remain. The role played by the surviving hair cells is not known. Many other questions remain unanswered at the present time. For example, what are the histopathologic correlates for successful and unsuccessful treatment as regards control of vertigo? Is there a clear and predictable relationship between total ototoxic dose and percent hair cell loss? What are the factors that determine cochlear ototoxicity? Quantitative studies on specimens from patients with well-documented clinical records who have received transtympanic and systemic aminoglycosides are necessary to better understand and refine the therapy for Meniere's disease.

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TEMPORAL BONE STUDIES OF THE HUMAN PERIPHERAL VESTIBULAR SYSTEM

4. MENIERE'S DISEASE

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Quantitative assessments of vestibular hair cells and Scarpa's ganglion cells were performed on temporal bones from 24 patients with well-documented Meniere's disease. Of these, 18 had unilateral disease and 6 had bilateral disease. Vestibular hair cell counts were made in each of the 5 sense organs by Nomarski (differential interference contrast) microscopy. Hair cell counts were expressed as densities: number of cells per 0.01 mm^2 surface area of the sensory epithelium. The results were compared with age- and sex-matched normal data. The type I hair cell densities for all vestibular sense organs were within the range for normative data. On the other hand, there was a significant loss ($p < .01$) of type II hair cells for all 3 cristae and both maculae. There was also a significant loss of Scarpa's ganglion cells ($p < .001$) when compared with normative data. The findings indicate a selective loss of type II hair cells and Scarpa's ganglion cells in Meniere's disease. These new observations have implications regarding the pathophysiological mechanism and clinical manifestations of Meniere's disease.

KEY WORDS — Meniere's disease, Scarpa's ganglion cells, temporal bone, vestibular hair cells.

INTRODUCTION

Meniere's disease is a unique disorder that apparently occurs only in humans. It is characterized by episodic vertigo, tinnitus, and aural fullness, and it has endolymphatic hydrops as its pathological correlate. Although there is no evidence that Meniere's disease occurs naturally in any nonhuman species, endolymphatic hydrops has been induced experimentally in many animals, most notably in the guinea pig, by the Kimura technique of obliteration of the endolymphatic duct.[1] Animal studies have shed considerable light on endolymphatic hydrops. However, one of their limitations is that animals with hydrops have never been shown conclusively to display signs of episodic vestibular disturbances. There are also considerable species differences, and some animals, such as monkeys and other primates, show little or no hydrops when the endolymphatic duct is obliterated. Hence, examination of human temporal bones from patients with Meniere's disease is essential to progress in understanding its pathophysiological mechanism and in developing effective therapies.

Previous qualitative observations of the vestibular sense organs and Scarpa's ganglion cells in light microscopic sections from patients with Meniere's disease have suggested that the vestibular hair cells and Scarpa's ganglion cells are preserved in most patients with Meniere's disease.[2] There has been only one study that has attempted a quantitative evaluation of the vestibular sense organs and Scarpa's ganglion.[3] Richter[3] concluded that there was no evidence for reduction in vestibular hair cells or Scarpa's ganglion cells in 11 temporal bones with endolymphatic hydrops. Richter's method of performing vestibular hair cell counts had certain limitations. The cytologic scoring criteria were subjective, and therefore, it is not clear whether hair cells and supporting cells were reliably differentiated from each other. His technique did not permit separate counts of type I hair cells and type II hair cells. Also, counts were made only on a single section for each vestibular sense organ in a given temporal bone. Thus, only a minute fraction of each sense organ was sampled.

The goal of this study was to perform a quantitative assessment of type I and type II vestibular hair cells and Scarpa's ganglion cells in temporal bones from patients with Meniere's disease. We previously developed a reliable and valid method of making these assessments[4] and have also gathered normative data on both hair cells and ganglion cells (this supple-

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TABLE 1. HAIR CELL DENSITIES IN VESTIBULAR SENSE ORGANS AND SCARPA'S GANGLION CELL COUNTS IN MENIERE'S DISEASE

				Superior Crista		*Lateral Crista*		*Posterior Crista*		*Utricle*		*Saccule*		
Age (y)	*Sex*	*Side*	*Duration of Symptoms (y)*	*Type I*	*Type II*	*Type I*	*Type II*	*Type I*	*Type II*	*Type I*	*Type II*	*Type I*	*Type II*	*Scarpa's Ganglion*
65	F	R	6	38	16	39	14	39	19	28	22	22	17	10,583
		L	6	32	10	28	12	32	10	33	22	19	16	10,815
78	M	R	13			40	14	43	13	39	16	27	11	17,530
		L	15	37	16	39	13	38	17	32	22	28	17	17,870
78	M	L	13											14,251
75	F	R	24	21	10	21	7	17	10	33	12	36	14	
		L	24	22	3	13	5	16	5			23	12	
62	M	R	4	37	19	39	14	39	17	32	17	21	17	17,530
		L	4	43	14	47	10	36	11	35	17	30	15	16,002
72	M	R	7	23	11	29	12	27	14	25	17	27	16	16,285
78	F	R	?	39	12	43	11	36	16	33	23	34	15	
		L	5	36	17	42	10	37	14	34	20	33	21	15,031
76	F	R	3	31	10	34	12	30	11	33	21	30	12	14,608
		L	3	34	11	36	9	37	9	33	14	27	12	13,006
44	F	L	6											10,666
53	M	R	6	39	11	46	10	44	6	35	18			21,771
86	F	R	1			33	16	29	12	34	17	32	15	19,510
86	M	L	20	34	11	34	7	33	6	36	8			
59	F	L	7											18,348
58	M	R	8	39	10	39	11	33	13	39	19			15,409
85	M	R	19											13,878
87	M	R	?	30	9	37	7			35	15	33	10	13,147
83	F	L	33	28	13	32	10	29	14	35	18			
80	M	L	23	41	9	39	12	37	8	34	15	30	12	18,946
66	M	R	10	43	10	45	7			31	16			13,807
53	M	L	16											21,762
67	M	L	5											16,289
86	F	R	26											17,996
62	M	L	2	39	8	39	4	38	7	32	13			22,854
74	M	R	12	36	6	35	6	36	5	41	15			15,981

Density data are hair cells per 0.01 mm^2.

ment, pages 3 and 14).

MATERIALS AND METHODS

Selection of Temporal Bones. The material for this study came from the temporal bone collection at the Massachusetts Eye and Ear Infirmary. These bones had been processed by the standard technique for study by light microscopy, which includes fixation, decalcification, celloidin embedding, serial sectioning in the axial plane at 20-μm thickness, and hematoxylin and eosin staining of every 10th section.[2] The collection was examined to select patients with Meniere's disease, defined as fluctuating sensorineural hearing loss and episodic vertigo documented in the medical history, and the occurrence of apparently idiopathic endolymphatic hydrops on light microscopy. Conditions such as otosyphilis that are known to cause similar symptoms were excluded. By these criteria, 24 subjects were identified. Of these, 18 had unilateral Meniere's disease and 6 had bilateral disease with both temporal bones available for study.

Quantitative Assessment of Vestibular Hair Cells and Scarpa's Ganglion Cells. Counts of type I, type II, and total (type I + type II) vestibular hair cells and of Scarpa's ganglion cells were performed with methods that we previously developed and described.[4] The hair cell counts are expressed as density, ie, the number of cells per 0.01 mm^2 of surface area of the sensory epithelium. Of the 30 temporal bones, hair cell density counts could be performed in 23 specimens and Scarpa's ganglion cells could be counted in 25 specimens. The measured hair cell densities and ganglion cell counts were then compared with age-matched control normative data (this supplement, pages 3 and 14).

Statistical Analyses. The various hair cell densities and Scarpa's ganglion cell counts were analyzed by means of a linear regression model. The model

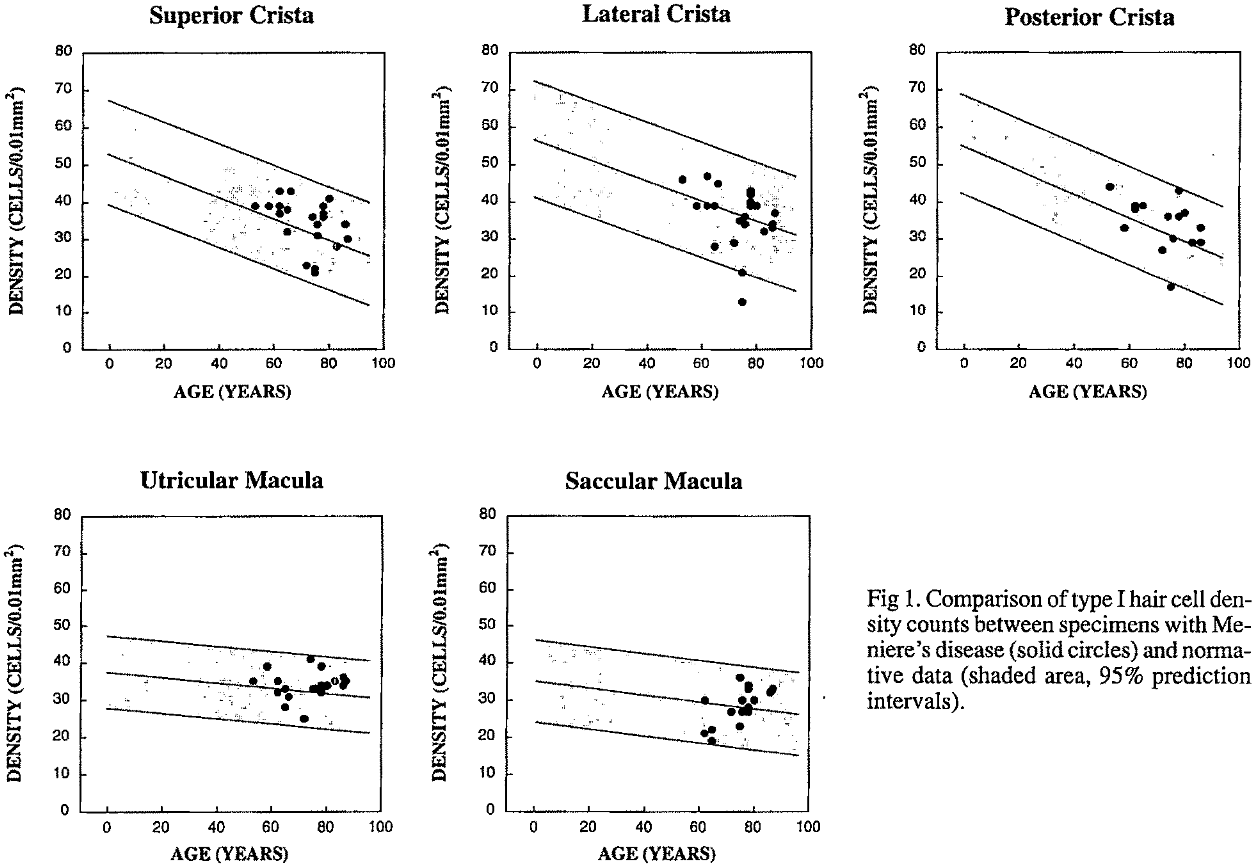


Fig 1. Comparison of type I hair cell density counts between specimens with Meniere's disease (solid circles) and normative data (shaded area, 95% prediction intervals).

adjusted for the effects of age and sex (as determined from the normative data reported in this supplement, pages 3 and 14). The model also included a random subject effect[5] to account for the fact that some individuals contributed 2 ears. A value of $p < .01$ (not .05) was used to indicate statistical significance in the present study, because of the large number of associations that were tested. In separate regression analyses, we examined whether the duration of Meniere's disease independently predicted a decline in hair cell densities in each sense organ, controlling for age and sex.

RESULTS

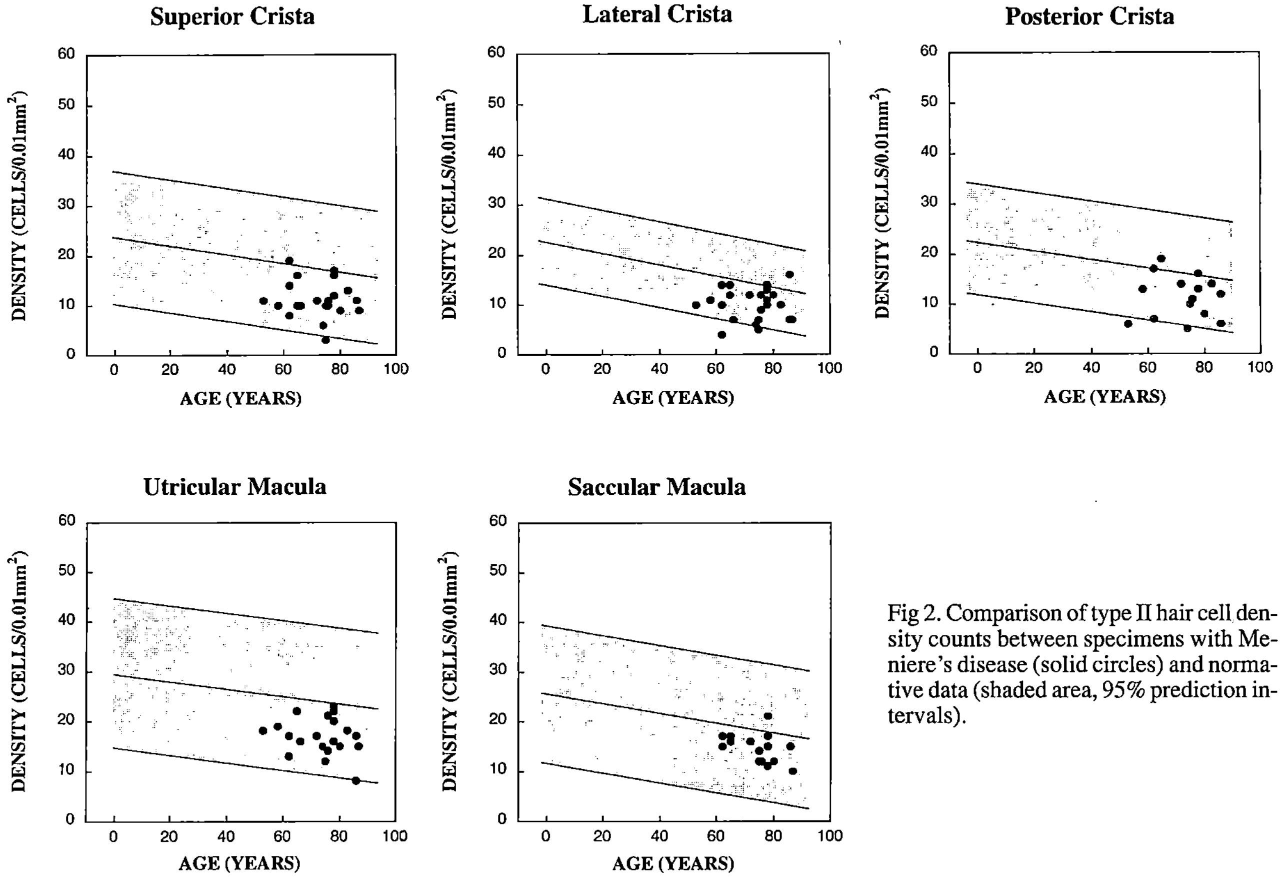
The raw data for type I and type II hair cell densities and for Scarpa's ganglion cell counts are shown in Table 1. Figures 1-4 compare the data for total, type I, and type II hair cell densities and for Scarpa's ganglion cell counts in Meniere's disease versus the 95% prediction intervals derived from age- and sex-matched normal data. Table 2 shows the results of the regression model analysis in which the effects of Meniere's disease on type I, type II, and total hair cell densities were analyzed for each of the 5 vestibular sense organs.

An analysis of the data in Table 2 shows that the total and type I hair cell densities were not significantly different from normative data for all sense organs. On the other hand, there was a significant reduction ($p < .01$) of type II hair cell densities in all 5 vestibular sense organs when compared with age-matched control data. There was also a significant loss of Scarpa's ganglion cells ($p < .001$) when compared with normative data.

The regression model was also used to assess the effect of the duration of symptoms on the loss of hair cells and Scarpa's ganglion cells. This analysis took into consideration the fact that there is a significant age-related loss of hair cells and Scarpa's ganglion cells in the normal population. There was no significant effect of duration on type I, type II, or total hair cell loss in any of the sense organs (Table 3) and no effect of duration on Scarpa's ganglion cell loss ($p = .76$).

DISCUSSION

Previous reports on human subjects with Meniere's disease have suggested that the vestibular hair cells and Scarpa's ganglion cells do not show significant losses at the light microscopic level.[2] Most of these previous studies were qualitative observations. The one quantitative study, by Richter,[3] was limited in its ability to discriminate hair cells from supporting cells, and type I from type II hair cells. The data of the present study show that there is a significant and selective reduction of type II hair cells in all 5 ves-


Superior Crista

Lateral Crista

Posterior Crista

Utricular Macula

Saccular Macula

Fig 2. Comparison of type II hair cell density counts between specimens with Meniere's disease (solid circles) and normative data (shaded area, 95% prediction intervals).

tibular sense organs and a significant loss of Scarpa's ganglion cells when compared with normative age- and sex-matched data. We offer the following hypothesis to explain the selective type II hair cell loss (L. Minor, personal communication, 1999). The basal and lateral surfaces of type II hair cells are bathed in perilymph and are therefore potentially susceptible to the influence of toxic metabolites in the perilymph. For example, potassium toxicity has been proposed as a mechanism for audiovestibular symptoms in Meniere's disease.[2] The type I hair cells, completely enveloped by the afferent nerve ending calyx that insulates them from the surrounding milieu, may be protected. The observed loss of Scarpa's ganglion cells may be hypothesized either to be the result of a primary neurotoxic effect (similar to the type II hair cell loss) or to be caused by retrograde neuronal degeneration secondary to type II hair cell loss. It should be noted that some studies of cochlear neurons from patients with Meniere's disease have shown a primary neuronal toxic effect.[6,7]

In the later stages of Meniere's disease, patients often experience chronic disequilibrium and often show reduced vestibular function as demonstrated by caloric hypoactivity and abnormal findings on rotational testing. The findings of the present study lead us to speculate that some of these symptoms of chronic disequilibrium and reduced vestibular function may be the result of the loss of type II hair cells, Scarpa's ganglion cells, or both. Other reports have suggested that distortion of the walls of the membranous labyrinth is responsible for these chronic symptoms and for the observed abnormalities on tests of vestibular function.[8,9]

Of relevance to this study is that the precise roles of type I and type II hair cells in vestibular sensory processing are not well understood. The type I and type II hair cells, which are morphologically quite different, also appear to be functionally distinct. For example, they have different filtering properties, different conductances, and different passive membrane properties.[10] The peripheral processes of Scarpa's ganglion (the afferent terminals) that innervate the hair cells can be classified into 3 morphological types.[11,12] Some afferent fibers end as calyces that innervate type I hair cells. Other afferent fibers give rise to several small bouton endings that innervate type II hair cells. The third type of fibers, so-called dimorphic fibers, provide a mixed innervation consisting of both calyces and boutons, with the calyces supplying type I hair cells and the boutons innervating type II hair cells. Although much has been learned about the discharge properties and other physiological functions of the vestibular afferent nerve fibers,

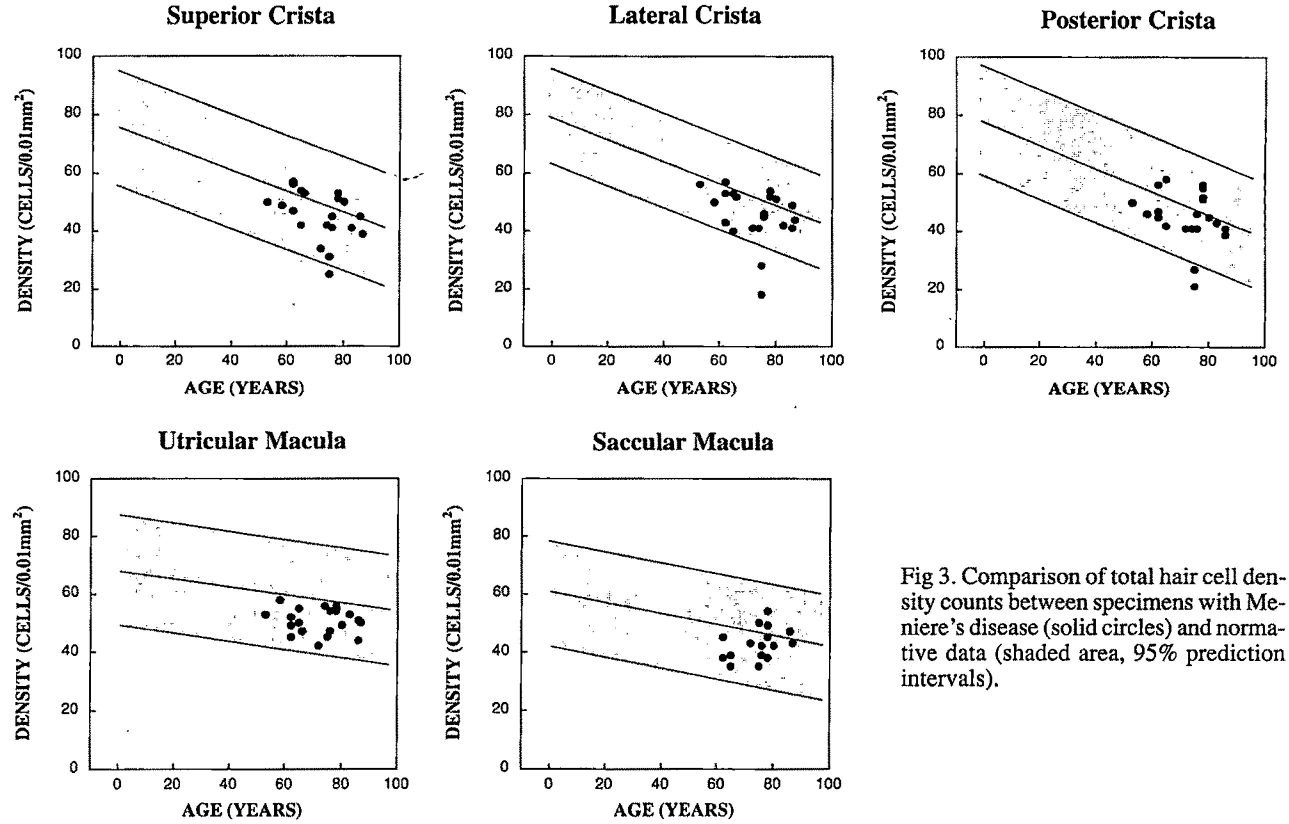


Fig 3. Comparison of total hair cell density counts between specimens with Meniere's disease (solid circles) and normative data (shaded area, 95% prediction intervals).

little progress has been made in determining the particular functions of type I and type II hair cells.[11] It is also known that the physiological properties of an afferent nerve fiber, including its discharge pattern, are more closely related to its epithelial location within the surface of the end organ than to the type of hair cell with which it makes contact. In other words, much remains to be discovered about the structure-function relationships within the vestibular end organs. Elucidation of the functions and physiological mechanisms of the hair cells and afferent nerve endings will undoubtedly help us to better interpret the findings of type II hair cell loss in Meniere's disease. In obtaining our hair cell data, counts were made on those parts of the sensory epithelium of the various end organs in which the plane of sectioning was at right angles. We deliberately did not make distinctions between hair cells at the summit versus the periphery of the cristae, in order to maximize the area that was sampled. However, it is possible to sample only the center and only the periphery and compare the loss of hair cells in one region versus the other in patients with Meniere's disease. The comparison may be of some relevance, given the importance of the spatial location of afferent nerve endings in determining the discharge properties.

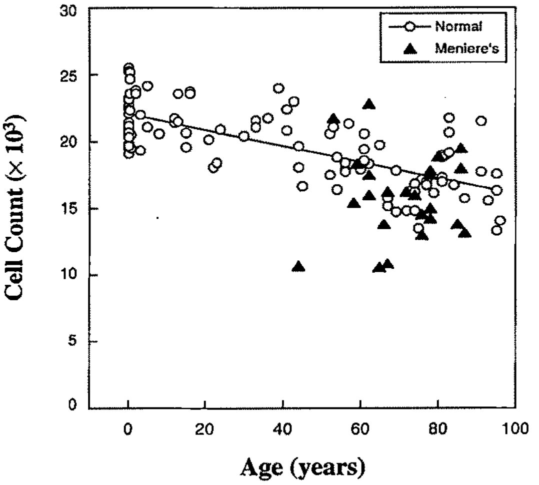


Fig 4. Comparison of Scarpa's ganglion cell counts between specimens with Meniere's disease and normative data.

We were unable to detect an effect of duration of

TABLE 2. RESULTS OF REGRESSION MODEL ANALYSES SHOWING EFFECT OF MENIERE'S DISEASE ON HAIR CELL DENSITY COUNTS

Sense Organ	*Type I Hair Cell Counts vs Normative Data*	*Type II Hair Cell Counts vs Normative Data*	*Total Hair Cell Counts vs Normative Data*
Superior crista	.16	.001*	.23
Lateral crista	.77	.004*	.03
Posterior crista	.35	.005*	.25
Utricle	.32	.0001*	.02
Saccule	.011	.009*	.21

Data are p values; * — p < .01.

TABLE 3. RESULTS OF REGRESSION MODEL ANALYSES SHOWING EFFECT OF DURATION OF SYMPTOMS ON HAIR CELL DENSITY COUNTS

Sense Organ	*Type I Hair Cell Counts*	*Type II Hair Cell Counts*	*Total Hair Cell Counts*
Superior crista	.18	.15	.10
Lateral crista	.02	.34	.03
Posterior crista	.04	.19	.03
Utricle	.59	.11	.33
Saccule	.72	.31	.43

Data are p values.

symptoms on hair cell or Scarpa's ganglion cell loss. The range of symptom duration was 1 to 33 years, with a mean of 11.3 years and a standard deviation of 8.56 years. Our regression analysis of the effect of duration controlled for age-related hair cell loss as seen in the normal population. Our sample size may have been too small and the disease duration too short for this study to demonstrate a significant effect of duration. On the other hand, it is also possible that the loss of type II cells and Scarpa's ganglion cells occurs early on in the disease and that the counts then remain relatively stable.

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MEDICAL MANAGEMENT OF ACUTE BACTERIAL SINUSITIS

RECOMMENDATIONS OF A CLINICAL ADVISORY COMMITTEE ON PEDIATRIC AND ADULT SINUSITIS

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ANNALS
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LARYNGOLOGY

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Acute sinusitis is commonly encountered in clinical practice and treated in the primary care setting. The clinician should recognize the subtle clinical presentation of acute bacterial sinusitis and initiate appropriate, aggressive treatment. Other upper respiratory tract disorders can confound the accurate diagnosis and appropriate treatment of sinusitis. Variable patterns of microbial resistance and antibiotic susceptibility and the dissociation between in vitro findings and clinical efficacy are a treatment challenge. This report is a comprehensive review of the pathophysiology and diagnosis of acute sinusitis, infectious agents, treatment methods, antibiotic resistance patterns, and costs associated with the management of sinusitis. Treatment algorithms are presented for adult and pediatric sinusitis.

KEY WORDS — amoxicillin, amoxicillin-clavulanate, antibiotic resistance, antimicrobials, cephalosporin, fluoroquinolone, *Haemophilus influenzae*, *Moraxella catarrhalis*, sinusitis, *Streptococcus pneumoniae*, trimethoprim-sulfamethoxazole

INTRODUCTION

Sinusitis is a common disorder that affects more than 30 million individuals each year in the United States.[1] About 90% of patients will visit their primary care physician for sinusitis treatment.[2] It is important for primary care physicians to be attentive to this condition because its incidence appears to be on the rise.[2] Prompt, effective therapy is required to reduce lost work time for adults and to permit children to return to school, allowing parents to return to work.[3] Antimicrobial resistance patterns have changed to create increasingly complicated problems with antimicrobial therapy.[4]

There are many pitfalls in accurately diagnosing acute bacterial sinusitis, one being overlaps with other upper respiratory tract diagnoses (allergies, viral infections, idiopathic rhinitis, fungal disease, neoplastic processes). The diagnosis of sinusitis is often presumptive and treatment is empirical, which presents further challenges to clinicians. The emergence of resistance and variable antibiotic susceptibilities of causative bacteria poses a greater challenge to antibiotic selection. Because sinusitis significantly impacts quality of life, clinicians should be aware of the trends in diagnosis and treatment of the acute condition.[5]

DEFINITION AND PATHOPHYSIOLOGY

Sinusitis encompasses a spectrum of acute and chronic, neutrophilic and eosinophilic, nonallergic and allergic inflammatory processes.[6] Bacterial sinusitis is an inflammation of the paranasal sinus mucosa caused by bacterial overgrowth in a closed cavity. This disorder is also called rhinosinusitis, because the nasal epithelium is continuous with the mucosa that lines the paranasal sinuses and the disease can affect both sites.[7] Viral or allergic rhinitis typically precedes sinusitis, and sinusitis without rhinitis is rare.[4,8] Many factors may predispose an individual to sinusitis (Table 1). Recent evidence shows that viral upper respiratory tract infections (URTIs) and pharyngeal colonization with group A streptococci predispose children to acute bacterial sinusitis.[9] It may be appropriate to select antibiotics that are also effective against group A streptococci, because *Streptococcus pyogenes* may be a concurrent infection in 15% to 20% of children.[9]

The maxillary, frontal, ethmoid, and sphenoid sinuses all drain into the nasal cavity through the ostia, which are approximately 1 to 3 mm in diameter (Fig 1). Obstruction of this narrow space may set up an environment for bacterial pathogens to colonize. Antibiotic use for acute obstruction is generally not indicated; however, if the obstruction persists for 7 to 10 days, secondary bacterial infection is likely. In acute bacterial sinusitis, a single bacterial species is responsible for the infection; however, multiple bacterial isolates were cultured in 26% and 30% of cases

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TABLE 1. FACTORS PREDISPOSING TO SINUSITIS

Prior upper respiratory tract infection
Concurrent group A streptococcal infection
Allergic rhinitis
Environmental pollutants (smoke)
Dental infections or extractions
Hormonal changes
Iatrogenic factors (mechanical ventilation, nasogastric tubes, nasal packing, dental procedures)
Anatomic variations (tonsillar and adenoid hypertrophy, deviated septum, nasal polyps, cleft palate)
Swimming
Immunodeficiency
Secretory disturbances (cystic fibrosis)
Immotile cilia syndrome
Abnormal mucociliary clearance secondary to ciliary structural abnormalities (Kartagener's syndrome)
Bronchiectasis
Asthma or acetylsalicylic acid–asthma–polyposis triad
Immature immune system
Adenoidal hypertrophy

in 2 studies, respectively.[10]

In addition to obstruction caused by inflammatory edema of the mucosa, viral and bacterial inflammation also decreases mucociliary activity, further compromising natural host defenses. Impaired ciliary transport results in stagnation of secretions, decreased pH, and lowered oxygen tension, providing a perfect medium for bacterial multiplication.[11]

Sinusitis is classified on the basis of duration of symptoms and anatomic location. Acute sinusitis symptoms last as long as 4 weeks.[12] Subacute sinusitis has minimal to moderate symptoms that are present for 4 to 12 weeks. Chronic sinusitis persists for more than 12 weeks and often has a pathophysiology that differs from that of acute sinusitis.[12] Chronic sinusitis represents an ongoing inflammation characterized by eosinophilia. The inciting agents of chronic sinusitis have been difficult to identify or prove.[4] Repeated damage of the mucosa in this condition causes loss of the normal state of sterility.[10] Recurrent sinusitis is defined as 4 or more episodes in 1 year, each episode lasting more than 7 days, with complete resolution between episodes.

The pathophysiology of sinusitis in children may be slightly different. Until recently, physicians assumed that sinuses were absent in infants and young children and often overlooked sinusitis in the pediatric population.[13] The ethmoid and maxillary sinuses are present and clinically significant at birth; however, the other sinuses develop more slowly. The sphenoid sinus develops between 3 and 7 years of age, and the frontal sinuses develop by 12 years of age. The sinuses continue to develop during childhood and adolescence.[14] In addition, the immune system is immature in children, making host reduction of bacterial load more difficult.[8] There is a lack of agreement about the clinical definition of sinusitis in children.[15]

EPIDEMIOLOGY, PREVALENCE, AND ECONOMICS OF SINUSITIS

Each year, approximately 16% of adults in the United States receive diagnoses of sinusitis. The incidence of sinusitis is higher in the Midwest and South, compared with the Northeastern and Western regions of the United States.[4] Rates of sinusitis are higher in the fall, winter, and spring months.[16] A National Center for Health Statistics annual survey estimated that 1 in 5 Americans has symptoms related to sinus disease and nasal allergies but does not seek medical attention.[17] Because many individuals do not seek medical help for this condition, the actual number of individuals affected may be much higher. Those who seek treatment account for an estimated 16 million office visits per year.[6,18] More than $2 billion is spent

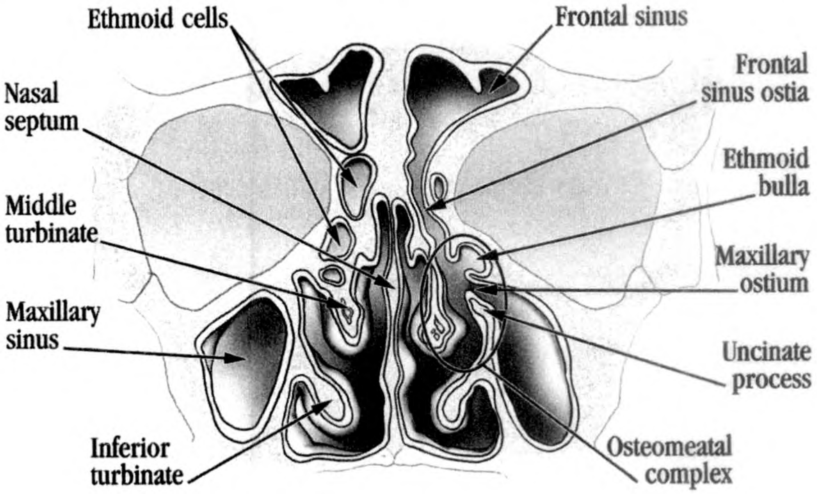


Fig 1. Diagram of paranasal sinuses.

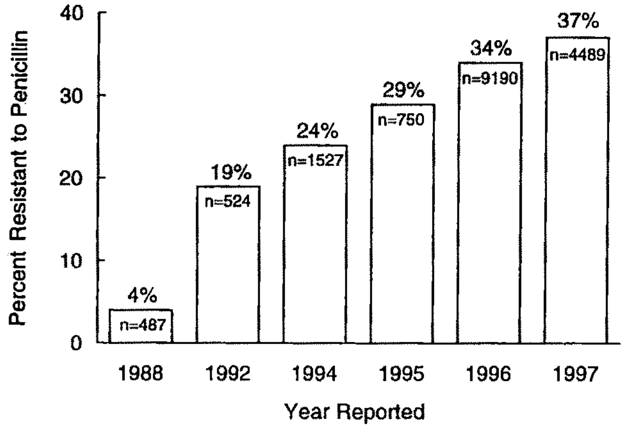


Fig 2. Increasing trend in *Streptococcus pneumoniae* penicillin resistance. Resistance is defined as either intermediate resistance (minimal inhibitory concentration of ≥0.12 µg/mL) or high resistance (minimal inhibitory concentration of ≥2 µg/mL).

annually for over-the-counter medications for sinusitis.[18] The National Ambulatory Medical Care Survey found sinusitis to be the fifth leading diagnosis for which providers prescribed an antibiotic.[19]

Because nasal symptoms are some of the most common complaints brought to primary care physicians, patients need to be informed that nonbacterial causes are most often the basis for symptoms such as rhinitis, nasal congestion, facial pressure, headaches, and postnasal discharge. Acute viral URTIs, seasonal allergic rhinitis, perennial allergic rhinitis, vasomotor rhinitis, and rhinitis medicamentosa have symptoms that overlap with acute bacterial sinusitis and are often a cause for misdiagnosis.[7] Physician compliance with patients' expectation of an antibiotic can result in indiscriminate antibiotic use. Studies show that 18% to 60% of patients with colds are prescribed antibiotics.[20-22] A Canadian survey found that approximately 50% of antibiotics were not indicated on the basis of evidence-based guidelines.[23] The reasons for overprescribing include physicians' education and experience, patient expectations, and economics.[24] However, studies of overprescribing may not have considered antibiotic use for prophylactic therapy, severity of illness, follow-up arrangements, or patient income variables.[25,26]

Viral rhinosinusitis is a more likely cause of nasal symptoms than any bacterial origin.[27,28] Viral rhinosinusitis occurs more often than bacterial sinusitis and does not require antibiotic treatment.[29] Although allergic rhinitis may be a predisposing factor in bacterial rhinosinusitis, it has not been clearly shown to cause bacterial rhinosinusitis in adults, and there is only a slight correlation in children.

Rhinosinusitis in children is a multifactorial disease. As the child becomes older, several predisposing factors change.[30] About 10% to 20% of children actually have allergic rhinitis, which may be present all year. Children 2 to 5 years of age average 6 to 8 URTIs per year.[31,32] Approximately 5% to 10% of these URTIs may become complicated by acute bacterial sinusitis.[33] Children in day-care centers have more frequent and longer-lasting respiratory tract infections because of superinfection.[34,35] Anatomic variations in children typically do not contribute to the prevalence of pediatric sinusitis.[36]

PATHOGENS IN SINUSITIS

The causative organisms of acute bacterial sinusitis are similar to those of acute otitis media. They include *Streptococcus pneumoniae* (30% to 40% of clinical isolates), *Haemophilus influenzae* (20% to 30%), *Moraxella catarrhalis* (12% to 20%), and *Streptococcus pyogenes* (up to 3%).[37] Other pathogens, found less frequently, include other *Streptococcus* species, *Staphylococcus aureus*, *Neisseria* species, and gram-positive and other gram-negative bacilli. Fungi are most commonly observed in immunocompromised and diabetic individuals. Anaerobic infections may occur in chronic sinusitis or with dental disease.[12]

Clinical studies in children with sinusitis are rare, because of the difficulties in diagnosing sinusitis in this age group. In the few pediatric studies published, the pathogens cultured from children with acute sinusitis and subacute sinusitis are similar to those of adults.[3,10] The predominant pathogens isolated from pediatric patients with chronic sinusitis are *S pneumoniae*, *M catarrhalis*, *H influenzae*, and anaerobes.[38-41]

ANTIBIOTIC RESISTANCE

The incidence of the bacterial species causing sinusitis has not changed in more than 4 decades; however, antimicrobial susceptibilities have changed within the past 2 decades.[12] Before 1980, more than 99% of pneumococcal strains were susceptible to penicillin. Recently, the prevalence of penicillin-resistant pneumococci has increased dramatically worldwide and shows a nearly twofold regional variation within the United States, approaching 33% to 58% of clinical isolates.[42,43] Data from US national surveillance studies showed a 4% resistance rate in the 1980s, which increased to 37% in 1997 (Fig 2).[44-50]

At least one third of *H influenzae* isolates and the majority of *M catarrhalis* isolates are β-lactamase–producing. Before 1972, *H influenzae* was almost uniformly susceptible to ampicillin. Since then, β-lactamase–producing strains resistant to ampicillin represent 30% to 40% of isolates.[51] *Moraxella catarrhalis*

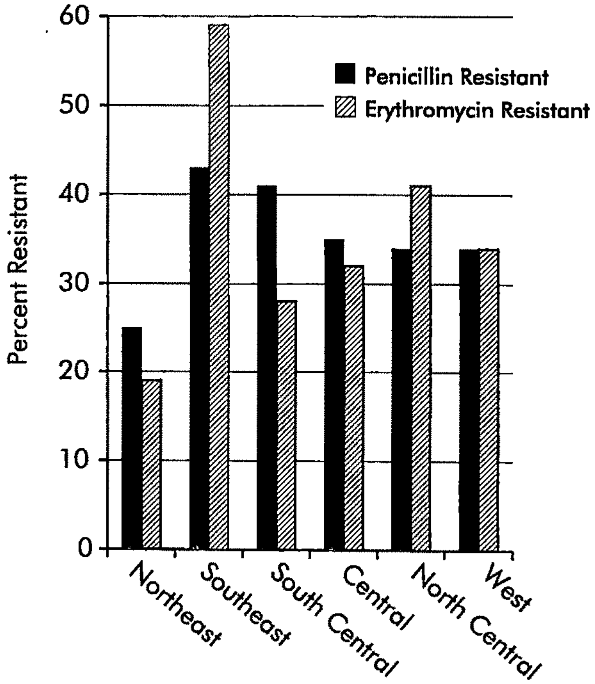


Fig 3. Prevalence of intermediately and highly resistant strains of *Streptococcus pneumoniae* in United States by region, September 1998 to February 1999.

was once uniformly susceptible to all agents, but is now commonly resistant. Wallace et al[52] reported a high rate of *M catarrhalis* resistance (>75%) due to the production of β-lactamase.[52] Doern et al[53] and Thornsberry et al[50] reported similar high rates of β-lactamase production in isolates of *M catarrhalis*: 95.3% and 92.7%, respectively.

The overuse of antibiotics, inappropriate dosing, and the use of broad-spectrum antibiotics as first-line treatment have contributed to the rising incidence of drug-resistant strains of bacteria. Resistance will continue to emerge and make our first-line agents less useful. Some penicillin-resistant strains display multidrug resistance to trimethoprim-sulfamethoxazole (TMP-SMX), macrolides, and some cephalosporins.

It is difficult to predict emerging resistance patterns. Antibiotic use in children is possibly a factor in emerging resistance, especially in day-care settings.[54] Several studies have shown that there are substantial rates of multidrug-resistant pneumococci among children in day-care settings.[55-58] Currently, it is estimated that greater than 50% of pneumococcal isolates from children in rural and urban day-care settings are resistant to penicillin.[55]

It is important for physicians to know the resistance patterns in their specific community. Four percent to 48% of *S pneumoniae* isolates are resistant to penicillin, depending on geographical area.[59] Geographical resistance patterns of *S pneumoniae*, *H influenzae*, and *M catarrhalis*, the 3 most common upper respiratory tract pathogens (a total of 4,979 clinical isolates), were studied in 52 independent and hospital laboratories across the United States from September 1998 to February 1999.[60] The standards and guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) were used for test methods. The United States was divided into 6 regions (Fig 3). Approximately one fourth of the *S pneumoniae* isolates tested against penicillin were resistant. In the Northeast and in the West, penicillin resistance rates were significantly lower. The rates of erythromycin resistance were similar to the rates of penicillin resistance. Although high resistance rates were noted across the country, significantly higher rates were noted in the Southeast. Thirty-one percent of *H influenzae* isolates produced β-lactamase. Ten strains were β-lactamase–negative and showed intermediate resistance to ampicillin. *Haemophilus influenzae* showed consistently high resistance rates to ampicillin across all regions and showed lower resistance rates to TMP-SMX, except in the Southeast. The resistance rates and positive β-lactamase production were consistent and alarmingly high across all regions, reaching 87% to 96% for *M catarrhalis*.

There is a direct correlation between β-lactamase production and the prior use of β-lactam antibiotics.[61] β-lactamase–producing bacteria and penicillin-resistant *S pneumoniae* appear to be more prevalent in the winter months than in the summer and fall months. In a study of patients from a suburban area in Washington, DC, the percentage of patients with oropharyngeal colonization with β-lactamase–producing organisms gradually increased from September to April and slowly decreased from April to August.[61]

Brook and others[62-64] have shown that the administration of some β-lactam antibiotics select β-lactamase–producing organisms in the respiratory tract. These organisms can spread within a family setting to other household members.[63] Prophylactic use of amoxicillin also selects penicillin-resistant organisms.[61]

INTERFERENCE PHENOMENON

The use of wide-spectrum antimicrobial agents may alter the normal upper respiratory tract flora. The use of such antibiotics may contribute to persistence of infection by inhibiting the nonpathogenic organisms in the upper respiratory tract that generally interfere with the growth of potential pathogens.[65,66] A comparative trial evaluated the effect of amoxicillin-clavulanate and cefprozil on the nasopharyngeal bacterial flora in children treated for acute otitis media.

Both agents were equally effective in eradicating the pathogenic organisms *S pneumoniae*, *H influenzae*, and *M catarrhalis*. Therapy with amoxicillin-clavulanate resulted in a significant decrease in the number of interfering, nonpathogenic bacteria, and cefprozil had only a minimal effect.[67] The nonpathogenic bacteria included α-hemolytic streptococci, *Prevotella melaninogenica*, and *Peptostreptococcus anaerobius*. The number of these interfering organisms was reduced at the end of therapy, from 50 to 11 after amoxicillin-clavulanate therapy, and from 50 to 42 after cefprozil therapy ($p < .001$). However, long-term follow-up was not performed in this study.

These interfering organisms are relatively resistant to second- and third-generation cephalosporins, but are susceptible to amoxicillin-clavulanate. The impact of antibiotics on normal flora that possess interfering capability toward pathogens needs further evaluation.

β-Lactamase–producing bacteria in the respiratory tract protect or shield penicillin-susceptible pathogens from inhibition by penicillin or amoxicillin.[68] β-Lactamase activity was detected in 12 sinus aspirates that harbored β-lactamase–producing bacteria in patients in whom antimicrobial therapy failed.[69]

DIAGNOSIS

Intranasal cultures are not indicative of the bacterial origin of acute sinusitis. The diagnosis of acute sinusitis is often difficult and is based on a careful, thorough history and physical examination. Although sinus aspiration and culture is the "gold standard" of diagnosis, the procedure is painful and may lead to iatrogenic infection. The majority of patients who visit a primary care physician for respiratory symptoms are likely to have a viral rather than a bacterial cause of sinusitis.[70,71]

Differentiating viral rhinosinusitis from bacterial sinusitis is often difficult, because viral rhinosinusitis often precedes bacterial sinusitis. In general, symptoms of bacterial sinusitis worsen after 5 days, persist for at least 10 days, and are more severe than those of viral disease.[72] About 0.5% of URTIs progress to sinusitis.[73,74] However, viral symptoms that persist for more than 7 days often establish an environment suitable for the development of bacterial infections and may predispose the patient to bacterial sinusitis.

The overall clinical impression is a more accurate diagnostic predictor of sinusitis than any single diagnostic predictor.[75,76] According to the Task Force on Rhinosinusitis of the American Academy of Otolaryngology–Head and Neck Surgery, diagnosis of acute sinusitis depends on the presence of at least 2 major diagnostic factors or 1 major factor and 2 minor factors (Table 2).[72] The number of diagnostic factors correlates with the likelihood that a bacterial infection is present.

TABLE 2. DIAGNOSTIC FACTORS PREDICTIVE OF SINUSITIS

Major factors
Facial pain or pressure (requires another major factor for diagnosis)
Facial congestion or fullness
Nasal obstruction
Nasal purulence or discolored postnasal discharge
Hyposmia or anosmia
Fever (acute sinusitis only)
Minor factors
Headache
Halitosis
Fatigue
Dental pain
Cough
Ear pain, pressure, or fullness
Fever (nonacute sinusitis)

Based on data from Lanza and Kennedy.[72]

A retrospective analysis found that family practice physicians relied on only 4 factors (sinus tenderness, facial pressure, postnasal drainage, and discolored postnasal drainage) to differentiate sinusitis from URTIs.[77] However, no particular sign or symptom is sensitive and specific for sinusitis.[75,78]

Relying on poor clinical predictors (ie, imprecise signs and symptoms) has significant implications for antibiotic use. Physicians need to evaluate and consider multiple diagnostic factors in sinusitis. Lindbaek et al[79] found the 4 symptoms and signs associated with a computed tomography (CT)–confirmed diagnosis of acute sinusitis to be 1) 2 phases in the illness history, 2) purulent rhinorrhea, 3) purulent secretions in the cavum nasi, and 4) an erythrocyte sedimentation rate greater than 10 mm. If 3 of these 4 signs and symptoms were present, the diagnosis had a specificity of 81% and a sensitivity of 66%. Although this sensitivity is higher than that of any individual clinical finding, the specificity is lower than that of maxillary edema (99%) or temperature greater than 38°C (89%).

Other complaints that may increase the probability of correctly diagnosing sinusitis include a recent prolonged URTI, a lack of response to decongestants, nasal airway obstruction, facial pain and pressure, sore throat, decreased sense of smell, and edema of the eyelid or chemosis.[80] In adults, purulent postnasal discharge and facial pain over the affected sinus that worsens with movement or percussion are cardinal symptoms.[81] Visualization of purulent nasal drainage on examination may be a strong indicator of acute sinusitis.[76] However, purulence does not differenti-

TABLE 3. VALUE OF SPECIFIC HISTORY, EXAMINATION, AND LABORATORY TEST PARAMETERS IN INITIAL DIAGNOSIS OF ACUTE SINUSITIS

Parameter	*Importance*
Patient history	
"Cold" present for more than 7 to 10 days	Significantly important
Unusually severe upper respiratory tract complaints	Significantly important
Fever	Significantly important
Mucopurulent discharge (>7 days)	Significantly important
Pain in upper teeth	Significantly important
Lack of response to over-the-counter decongestants	Significantly important
Dull headache	Variable importance*
Clinical assessments	
Unilateral or bilateral tenderness in midface region	Significantly important
Inspection of nasal mucosa	Significantly important
Facial tenderness	Significantly important
Intranasal pus	Significantly important
Purulent postnasal mucus in pharynx	Significantly important
Transillumination	Not significantly important
Diagnostic tests	
Radiographs (Waters' view)	Variable importance*
Radiographs (3 views)	Not significantly important
Sinus aspiration, when indicated	Significantly important
Computed tomography†	Not significantly important
Anterior rhinoscopy	Significantly important
Ultrasound	Not significantly important
Magnetic resonance imaging	Not significantly important
Fiberoptic nasal endoscopy	Variable importance*
Nasal mucus smear	Not significantly important
Immunologic screen	Not significantly important
Cultures from sinus puncture (when indicated)	Significantly important
Erythrocyte sedimentation rate	Not significantly important

*Important only in context of other signs, symptoms, and patient history in whole picture of clinical assessment.

†Chronic infection or complications pending.

ate between a viral origin and a bacterial origin.

Anterior rhinoscopy is very important and can be performed with a nasal speculum or otoscope. The use of a topical decongestant before the examination may improve the field of view. The examination should include viewing the turbinates and septum, evaluating the quality of the mucus, and determining the presence of polyps and bleeding.

Symptoms in children are different from those in adults and are difficult to distinguish from those of the common cold or vasomotor rhinitis. They are more nonspecific and may include rhinorrhea, nasal congestion or obstruction, fever, purulent anterior or posterior nasal discharge, snoring, mouth breathing, feeding problems, bad breath, cough, and hyponasal speech.[13,15] The most common complaints are cough and nasal discharge. The classic signs and symptoms found in adults (eg, facial pain and headache) are rare.[82] Pediatric acute sinusitis must be differentiated from allergic rhinitis, which is characterized by continuous stuffiness, sneezing, itchy eyes, and a family history of atopy. Adenoidal hypertrophy or a severely deviated nasal septum may also contribute to symptoms. The presence of a foreign body, asthma, or neoplasm must be ruled out.[13]

Further diagnostic testing and imaging should be performed for atypical cases and treatment failures. No imaging studies are recommended for the routine diagnosis of uncomplicated sinusitis presented to the primary care physician.[83] The diagnostic value of sinus radiographs is limited by poor sensitivity and specificity. Radiologic evidence of sinusitis is frequently found in patients with viral rhinitis.[84] The Waters' view may offer the simplest demonstration of fluid accumulation in the maxillary sinus. Although the presence of opacification or air-fluid levels in the sinuses is fairly predictive of bacterial infection, it is seen in only 60% of patients with acute sinusitis.[85] If mucosal thickening is included as an indication of sinusitis, the specificity can be as low as 36%.[86]

Researchers conclude that transillumination has limited diagnostic use and depends on the clinician's skill level.[75] As a single finding, transillumination cannot be relied on to confirm or rule out the diagnosis.[87] Ultrasound also has limited diagnostic value.

A CT scan should be reserved for patients who re-

TABLE 4. RISK FACTORS PROMPTING USE OF SECOND-LINE AGENT

Antibiotic use in past month
Resistance common in community
Failure of first-line agent
Infection in spite of prophylactic treatment
Smoker in family
Child in day-care facility
Younger than 2 years of age
Patient history
Allergy to penicillin or amoxicillin
Frontal or sphenoidal sinusitis
Complicated ethmoidal sinusitis
Presentation with protracted (>30 days) symptoms

spond inadequately to medical therapy, have numerous bacterial infections throughout the year, or have a history of polyposis. Most patients with a viral URTI who undergo a CT scan will demonstrate evidence of sinusitis, and therefore, the value of CT scanning in diagnosis is questionable. However, CT scanning is useful in identifying the underlying cause of chronic infection and in identifying the sinuses involved and any complications that may exist. The CT scans should be performed in a coronal view, and a limited series is usually adequate. Contrast enhancement is not recommended unless there is a central nervous system complication. Table 3 presents the value of specific history, examination, and laboratory test parameters in the initial diagnosis of acute sinusitis.

ANTIMICROBIAL THERAPY

Although 40% of sinusitis patients will recover spontaneously, antibiotics are indicated in the treatment of correctly diagnosed acute sinusitis.[4,37,51] Hueston et al[77] noted that 3 of 4 randomized trials support the use of antibiotics in treating acute sinusitis. Sinusitis is treated empirically because of the invasive nature of culturing the paranasal sinuses. Comparative trials have shown minimal evidence of the superiority of one antibacterial agent over another.[16,88] Effective antibiotic therapy often produces a more rapid resolution of symptoms.[7,89]

The goal of treatment is to arrest the acute infection before it progresses and to prevent serious sequelae (eg, facial osteomyelitis, cavernous sinus thrombosis, meningitis, orbital cellulitis or abscess, or brain abscess).[90,91] Most importantly, appropriate use of antibiotics may decrease the rate of complications, as well as prevent the progression of acute sinusitis to chronic sinusitis through a more rapid reduction of tissue edema and bacterial contamination and the reestablishment of drainage and ventilation of the sinus cavity. Treatment is thought to prevent permanent mucosal damage.[80] Clayman et al[92] found the rate of intracranial complications from acute sinusitis to be 3.7% in adults. Lerner et al[93] found a similar incidence (3.0%) in children. Despite adequate antibiotic treatment, the mortality rate (30%) and the morbidity rate (60%) from cavernous sinus thrombosis remain high in adults and slightly better in children.[94]

Treatment of bacterial sinusitis usually begins with an inexpensive first-line agent (eg, amoxicillin or TMP-SMX). A recent analysis of in vitro data suggests that current doses of amoxicillin may not be adequate for eradication of intermediately and fully resistant *S pneumoniae*. It is recommended that the amoxicillin dose be doubled (up to 80 to 90 mg/kg per day; maximum of 3 g/d), especially in areas in which resistance to *S pneumoniae* is high. The clinical benefit of using higher doses of amoxicillin still needs to be evaluated in clinical trials.[95] In many geographic areas, the resistance of *S pneumoniae* to TMP-SMX is higher than that to penicillin. Resistance of *H influenzae* to TMP-SMX has increased significantly in recent years.[96] Second-line agents should be used when resistant pathogens are suspected. Table 4 lists the risk factors.

Choosing a second-line antibiotic depends on proven clinical efficacy, resistance patterns, dosing schedules, the adverse events profile, the potential for compliance, knowledge of patient allergies, the previous response history, the physician's experience with agents, and the cost-benefit ratio. Antibiotic choice based on pharmacokinetic properties alone may be misguided. Although the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) have been the gold standards for measuring drug activity, they provide only partial information. The MIC and MBC are useful predictors of drug-organism interaction in a static system, but they do not provide information on the time course of microbial exposure to an antibiotic.[97] For β-lactam antibiotics, vancomycin, clindamycin, and the macrolides, activity depends on the time of exposure to the drug, at low multiples of the MIC, rather than peak drug concentration. In sinusitis treatment with β-lactam antibiotics (amoxicillin and cephalosporins), time of exposure is critical. In animal infection models, time above MIC has been the only pharmacodynamic parameter to correlate with the clinical efficacy of β-lactam antibiotics.[97] A nationwide surveillance study evaluating 4,489 clinical isolates of *S pneumoniae* for their susceptibility to various antimicrobial agents determined that penicillin susceptibility had a significant impact on time above MIC.[98] Plasma levels of cefprozil, cefaclor, cefixime, cefpodoxime proxetil, and cefuroxime axetil exceeded the geometric mean

TABLE 5. ANTIBIOTICS USED FOR SINUSITIS AND LIKELIHOOD OF EFFECTIVENESS ACCORDING TO PHARMACODYNAMIC AND PHARMACOKINETIC PARAMETERS

		Streptococcus pneumoniae			Haemophilus influenzae		
Antibiotic	*Adult Dosage*	*S*	*I*	*R*	*BL−*	*BL+*	Moraxella catarrhalis
First line							
Amoxicillin (Amoxil, Trimox, Wymox)	250-500 mg tid	+++	++	−	++	−	−
TMP-SMX (Bactrim, Septra)	160 mg/800 mg bid	++	−	−	++	+	+
Second line							
β-Lactams							
Cefpodoxime proxetil (Vantin)	200-400 mg bid	+++	+	−	++	++	+++
Cefprozil (Cefzil)	250-500 mg bid	+++	++	−	++	++	+++
Cefuroxime axetil (Ceftin)	250-500 mg bid	+++	++	−	++	++	+++
Cefdinir (Omnicef)	300 mg bid	+++	+	−	+++	+++	+++
Amoxicillin-clavulanate (Augmentin)	250-500 mg tid* 500-875 mg/kg bid*	+++	+	−	+++	+++	+++
Third line							
Macrolide							
Azithromycin (Zithromax)	250 mg qd	+++	±	−	++	+	++
Clarithromycin (Biaxin)	500 mg bid	+++	±	−	++	±	+
Fluoroquinolone							
Ciprofloxacin (Cipro)	500-700 mg bid	++	±	−	+++	+++	+++
Levofloxacin (Levaquin)	500 mg qd	+++	+++	+++	+++	+++	+++
Gatifloxacin (Tequin)	400 mg qd	+++	+++	+++	+++	+++	+++
Moxifloxacin (Avelox)	400 mg qd	+++	+++	+++	+++	+++	+++
Other							
Clindamycin (Cleocin)	150-450 mg tid or qid	+++	++	++	−	−	−

S — penicillin-sensitive, I — intermediate resistance to penicillin, R — penicillin-resistant, BL− — β-lactamase–negative, BL+ — β-lactamase–positive, tid — 3 times daily, bid — twice daily, qd — once daily, qid — 4 times daily, +++ — excellent coverage, ++ — good coverage, + — fair coverage, ± — minimal coverage or efficacy, − — no significant activity, TMP-SMX — trimethoprim-sulfamethoxazole.

*Based on amoxicillin component.

MIC for penicillin-susceptible *S pneumoniae* during 40% of the dosing interval. However, with intermediately penicillin-resistant strains, only cefprozil, cefuroxime axetil, and cefpodoxime proxetil achieved similar concentrations for a similar duration — a finding that suggests that these 3 cephalosporins provide the most reliable pharmacodynamic profiles against penicillin-susceptible and intermediately penicillin-resistant strains.

Other factors to consider include the rate of bactericidal activity, enhancement by increasing drug concentration, and persistent effects, which include postantibiotic effects, postantibiotic sub-MIC effects, and postantibiotic leukocyte enhancement. In vitro measurements may be significantly different from the in vivo response. Focusing only on laboratory pharmacokinetic data discounts the synergistic effect afforded by the actions of host defense mechanisms and bacterial load reduction by the antibiotic.

Table 5 illustrates the antibiotics used in the empiric treatment of acute sinusitis and their effectiveness against *S pneumoniae*, *H influenzae*, and *M catarrhalis*. Penicillin, erythromycin, cephalexin, tetracycline, and cefixime are not generally recommended for the treatment of sinusitis, because of the inadequacy of their spectrum of activity.

Although the cephalosporins offer broad coverage in treating sinusitis, they have varying activities and must be evaluated on an individual basis. The first-generation agents have poor *H influenzae* coverage. Cefaclor, a second-generation agent, has better coverage, but resistance in *H influenzae*, *M catarrhalis*, and *S pneumoniae* is a growing problem. In addition, 3-times-daily dosing is often required, which can affect compliance, and there is a risk of serum sickness–like reactions with cefaclor.[99] Cefadroxil has poor activity against certain gram-negative bacteria and *S pneumoniae*. The use of antibiotics with suboptimal activity has the potential to hasten the emergence of resistant bacteria and is highly discouraged.[4]

Several second- and third-generation cephalosporins that have excellent activity against all major pathogens include cefprozil, cefuroxime axetil, and cefpodoxime proxetil. All are effective in twice-daily dosage and provide adequate coverage of β-lactamase–producing organisms. These 3 cephalosporins are listed in Tables 5 and 6 because they maintain rela-

TABLE 6. FEATURES OF ANTIBIOTICS TO CONSIDER IN SELECTION OF ANTIMICROBIAL AGENTS FOR ACUTE SINUSITIS

Antibiotic	*Advantages*	*Disadvantages*
Amoxicillin	Inexpensive Good tolerance Extensive clinical experience	Not effective against β-lactamase–producing organisms Possible activity against normal flora
Amoxicillin-clavulanate	Effective against β-lactamase–producing organisms Twice-daily dosing Active against aerobic and anaerobic respiratory pathogens	Higher rate of cramping and diarrhea No added benefit over amoxicillin alone when treating infections caused by penicillin-resistant strains of *S pneumoniae* Possible activity against normal flora
Trimethoprim-sulfamethoxazole	Used for penicillin-allergic patients Some activity against *H influenzae* Twice-daily dosing Inexpensive Particularly effective against gram-negative organisms	Resistance by group A *Streptococcus* Variably effective against *H influenzae* and *S pneumoniae* Can cause blood dyscrasias, sulfa hypersensitivity, and rashes
Cefuroxime axetil	Good spectrum of activity Twice-daily dosing	Can cause diarrhea and nausea Suspension formulation has bitter taste High relative rate of *C difficile* Expensive
Cefdinir	Good spectrum of activity Once-daily dosing	Activity against penicillin-intermediate and penicillin-resistant strains of *S pneumoniae* not well studied Higher rate of diarrhea
Cefpodoxime proxetil	Spectrum of activity Twice-daily dosing	Higher rate of *C difficile* Higher rate of diarrhea, nausea, vomiting, abdominal pain Metallic aftertaste
Cefprozil	Good spectrum of activity Twice-daily dosing Good-tasting oral suspension Low incidence of side effects	Not as high in vitro activity against β-lactamase–producing strains of *H influenzae*
Azithromycin	Once-daily dosing Alternative for penicillin-sensitive patients Long half-life allows shortened course of therapy	30%-60% of *S pneumoniae* and *H influenzae* strains resistant or not eradicated
Clarithromycin	Twice-daily dosing Alternative for penicillin-sensitive patients Fewer gastrointestinal adverse effects compared to erythromycin	Interacts with theophylline, terfenadine, and astemizole Marginal activity against *H influenzae* Metallic aftertaste
Ciprofloxacin	Broad coverage of gram-negative and atypical organisms	Marginal activity against *S pneumoniae* Higher rates of diarrhea, nausea, headache Safety not established in children younger than 18 years of age Poor gram-positive coverage
Levofloxacin	Once-daily dosing Broad coverage of gram-negative, gram-positive, penicillin-resistant *S pneumoniae*, and atypical organisms	Broad spectrum of activity Not indicated in children
Moxifloxacin	Once-daily dosing Improved gram-positive coverage over older quinolones, especially against *S pneumoniae* and atypical organisms	Broad spectrum of activity Not indicated in children
Gatifloxacin	Once-daily dosing Improved gram-positive coverage over older quinolones, especially against *S pneumoniae* and atypical organisms	Broad spectrum of activity Not indicated in patients younger than 18 years of age
Clindamycin	Good activity against penicillin-resistant *S pneumoniae* and anaerobic bacteria	Higher rate of diarrhea, gastrointestinal upset Can increase risk of *C difficile* infection Not active against gram-negative aerobic bacteria

TABLE 7. FREQUENCY OF POSITIVE TESTS FOR *CLOSTRIDIUM DIFFICILE* DIARRHEA

Antibiotic	*No. of Risk Periods**	*Positive Test*	
		No.	*%*
Amoxicillin	39	7	17.9
Cefixime	9	5	55.6
Cefaclor	4		
Cefuroxime	22	9	40.9
Cefprozil	8		
Cephalexin	16	9	56.3
Ciprofloxacin	15	1	6.7
Clarithromycin	2		
Amoxicillin-clavulanate	25	9	36.0
Clindamycin	1		
Erythromycin-sulfisoxazole	2		
Trimethoprim-sulfamethoxazole	20	2	10.0

*Risk periods for which *Clostridium difficile* tests were performed. Data from Levy et al.[101]

tively high levels of activity against intermediate-level resistant pneumococci.[12] Cefpodoxime proxetil has good activity against *H influenzae* and *M catarrhalis*; however, its metallic aftertaste can compromise patient compliance. Cefixime, loracarbef, and ceftibuten are not included on Tables 5 and 6 because of their reduced activity against *S pneumoniae*, which may compromise clinical efficacy.[100] However, cefixime and ceftibuten can be combined with another agent (ie, clindamycin) to cover *S pneumoniae*.

The risk of *Clostridium difficile* diarrhea is another consideration in patients being treated with prolonged courses of antibiotic therapy. Although it is commonly described in association with substantial morbidity in hospitalized patients, it can occur in the ambulatory care setting. The risk of *C difficile* diarrhea was recently evaluated in a retrospective longitudinal study of 4 large managed-care health plans.[101] The analysis identified patients with a claim indicator for a *C difficile* toxin test. A single antibiotic group was identified in 217 enrollees in the analysis (Table 7[101]). Cephalexin and cefixime had the highest frequencies of positive *C difficile* tests, which were 56.3% and 55.6%, respectively. Cephalexin and cefixime showed a statistically significant association with *C difficile* diarrhea, and amoxicillin-clavulanate and cefuroxime showed a trend toward an increased risk for *C difficile* diarrhea. In this study, antibiotics that demonstrated minimal association with positive *C difficile* tests included cefaclor, cefadroxil, and cefprozil.

Antibiotic resistance may be caused by a variety of mechanisms (eg, enzymatic degradation or altered antibiotic binding sites). β-Lactamase–producing organisms cause enzymatic degradation of antibiotics with a β-lactam moiety in their chemical structure. Clavulanate is a β-lactamase inhibitor; therefore, amoxicillin-clavulanate is effective against β-lactamase–producing organisms (eg, β-lactamase–producing strains of *H influenzae* and *M catarrhalis*).

The mechanism of *S pneumoniae* resistance is different from that of β-lactamase production. *Streptococcus pneumoniae* resistance occurs because of an altered penicillin binding site. Amoxicillin-clavulanate offers no advantage over amoxicillin alone in the treatment of infections caused by resistant strains of *S pneumoniae*.

As previously discussed, higher routine doses of amoxicillin may be needed in certain circumstances. A common recommendation is to double the usual dose. With currently available formulations of amoxicillin-clavulanate, 2 prescriptions are required (1 for amoxicillin and the other for amoxicillin-clavulanate) to achieve a higher dose of amoxicillin without increasing the dose of clavulanate, a gastrointestinal mucosal irritant. The complexity of such a regimen may compromise patient compliance.

The newer macrolides (clarithromycin and azithromycin) may be acceptable second-line agents, specifically in patients who are allergic to penicillin. Resistance among the pneumococci to these agents is increasing.[50,96] Breakpoints for resistance by the NCCLS are ≥1 μg/mL for erythromycin and clarithromycin and ≥2 μg/mL for azithromycin, although the NCCLS recommends that erythromycin antimicrobial susceptibility test results can predict the activities of other macrolides. Erythromycin-resistant strains are resistant to clarithromycin, azithromycin, and usually penicillin.[102] *Haemophilus influenzae*, which is susceptible in vitro to azithromycin, may survive in an infected fluid because of lower extracellular concentration of the antibiotic.[103] The mechanisms of action of macrolide resistance may be enzymatic deactivation or active efflux of the antibiotic across the bacterial cell membrane or ribosomal alterations.[104,105] Clindamycin can be used for infections caused by *S pneumoniae*, but it does not eradicate *H influenzae* or *M catarrhalis* and is consequently inappropriate empirical therapy for sinusitis.

The newer fluoroquinolones — levofloxacin, moxifloxacin, and gatifloxacin — have good in vitro activity against *S pneumoniae*, including penicillin-resistant isolates, and excellent tissue penetration into the sinuses. The first-line use of the fluoroquinolones should be restricted to patients with moderate-to-severe infections or recent antibiotic failures. There are differences between the in vitro activities of the different fluoroquinolones against *S pneumoniae*.[106,107]

Gatifloxacin and moxifloxacin have greater in vitro activity than levofloxacin when tested against *S pneumoniae*. The newer fluoroquinolones offer once-daily dosing and have low phototoxic potential.[108-110] Currently, the fluoroquinolone antibiotics are not indicated for patients younger than 18 years of age. The role of these agents has not been clearly established in the treatment of acute sinusitis. Emerging reports of fluoroquinolone resistance among pneumococci underscore the need to curtail the inappropriate use of these drugs for infections that can be treated with β-lactam or macrolide antibiotics.[106]

The Joint Task Force on Practice Parameters for Allergy and Immunology has developed guidelines to aid the clinician in therapeutic decision-making.[111] This comprehensive document covers every major aspect of sinusitis in various formats, and it is the basis for the treatment algorithms for selecting antimicrobial therapy (Figs 4 and 5). Sinusitis can be classified as acute (<4 weeks), subacute (4 to 12 weeks), or chronic (>12 weeks). Antibiotic therapy should be considered for acute sinusitis if the acute illness has persisted for more than 7 days, or less than 7 days in patients with fever and headaches who are not responsive to analgesic management, and for subacute sinusitis cases. An initial otolaryngological consultation is recommended for chronic sinusitis.

The initial choice of antibiotic should begin with amoxicillin or TMP-SMX and consider cost, bacterial resistance patterns in the locality, the severity and duration of infection, and risk factors prompting consideration of a second-line agent. The choice of a second-line antibiotic also should include proven efficacy, an allergic history, the previous response to the selected antibiotic, and the physician's experience. In all cases, the selection of an antibiotic should be tempered by patient-focused considerations.

DURATION OF THERAPY

The symptoms should abate within a few days after the initiation of treatment, and 10 to 14 days is considered an adequate treatment interval. A longer treatment interval may be warranted if symptoms persist. Researchers have looked at shorter courses of antimicrobial treatment to lower costs, reduce side effects, increase compliance, reduce the potential for resistance, and decrease the impact on commensal flora.[112] Although the results of these studies are promising, further studies of short-course therapy are needed, especially in children, and clinical judgment is paramount.

The majority of patients with sinusitis are treated on an outpatient basis that necessitates appropriate follow-up to assess compliance.[113] Follow-up times vary widely according to the patient's age, risk factors, and history.[114] Additional evaluations are necessary if symptoms persist or worsen, perhaps because of resistant bacteria or poor antimicrobial coverage. Children should be considered at greater risk for recurrence if they are younger than 6 months of age, attend day care, live with a smoker, or have a history of multiple URTIs.

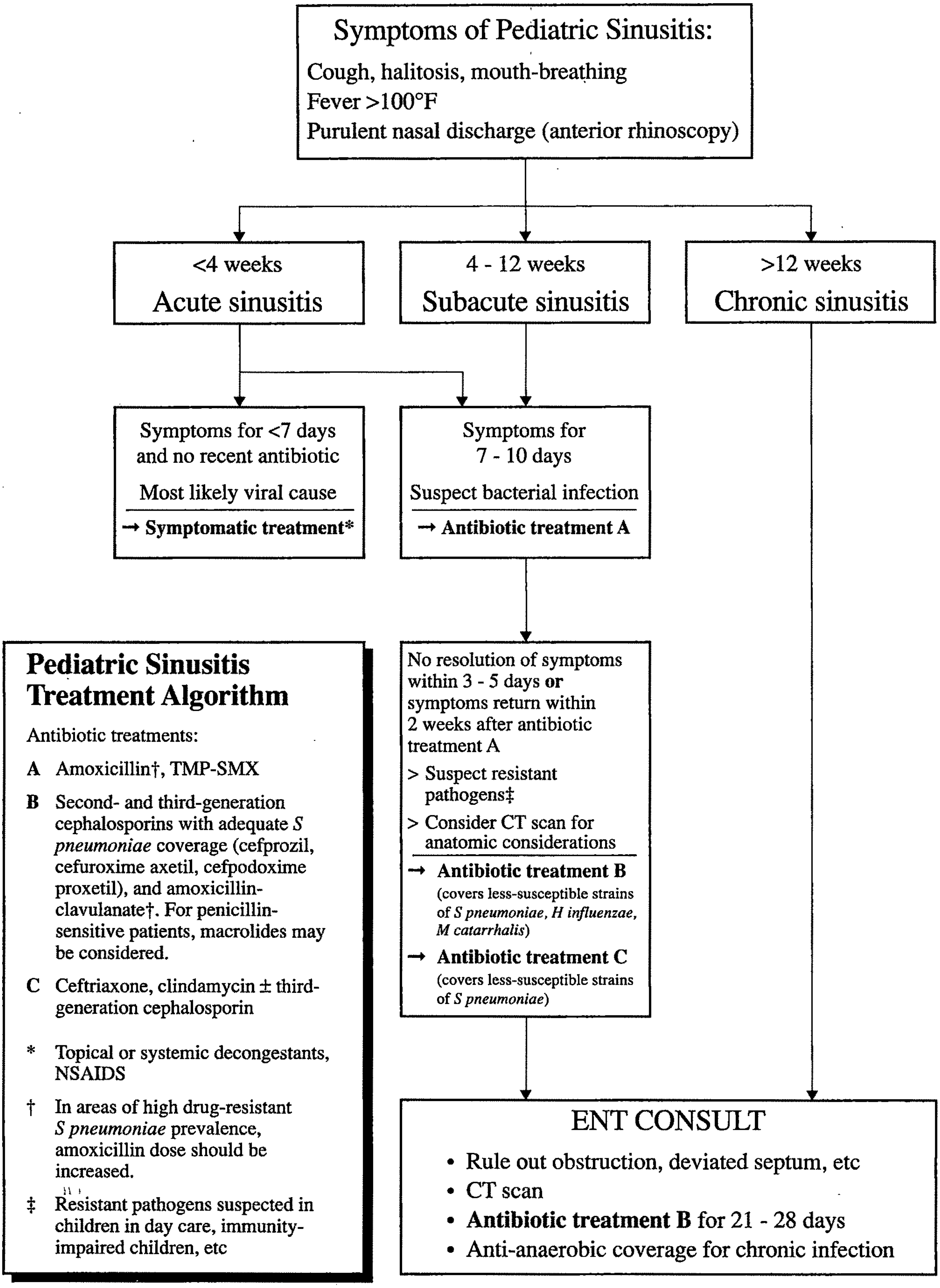
Physicians should consider immunologic defects in children who do not respond to treatment. The majority of children who have severe sinusitis have inadequate humoral defenses[115] and prolonged courses of antibiotics. The use of antibiotics in children is controversial. Many cases resolve spontaneously, whereas others tend to progress; antibiotic use should be limited to highly selected patients.[29] Antibiotics should be used in children whose signs and symptoms persist for 10 to 14 days or longer without improvement.[33,82]

ADJUNCTIVE TREATMENTS

Adjunctive treatments are designed to promote ciliary function and decrease edema. Although most are unproved, these measures are not expensive, complicated, or associated with major side effects. Hence, they represent reasonable supportive measures. Saline nasal sprays, humidifiers, warm aerosols, steam, aromatic vapors, hot soups, and teas moisturize the nasal cavity and remove thick mucus crusts and thus help minimize symptoms.

Topical decongestants (eg, phenylephrine hydrochloride, oxymetazoline hydrochloride) relieve nasal congestion by stimulating mucosal α-adrenergic receptors, thereby shrinking the edematous mucosa and relieving obstruction.[116] The use of these sprays should be limited to 3 days to avoid rhinitis medicamentosa, which can worsen nasal congestion. Systemic decongestants (eg, pseudoephedrine, phenylpropanolamine hydrochloride) may reduce nasal congestion, but typically have side effects that include insomnia or hyperactivity. The use of systemic decongestants is not recommended in children, especially when there is a potential for cardiac stimulation, hypertension, or neurologic complications.[13,117,118]

Studies in adults show that when decongestants are prescribed in conjunction with antibiotics, both symptoms and total costs decrease — a finding suggesting that physicians should consider this dual approach to treating sinusitis.[119] The expectorant guaifenesin, 1,200 mg twice daily in adults, can help thin secretions and improve ciliary action, thus lessening mucus stasis and improving drainage.


Symptoms of Pediatric Sinusitis:
Cough, halitosis, mouth-breathing
Fever >100°F
Purulent nasal discharge (anterior rhinoscopy)
<4 weeks
Acute sinusitis
4 - 12 weeks
Subacute sinusitis
>12 weeks
Chronic sinusitis
Symptoms for <7 days and no recent antibiotic
Most likely viral cause
→ Symptomatic treatment*
Symptoms for 7 - 10 days
Suspect bacterial infection
→ Antibiotic treatment A
No resolution of symptoms within 3 - 5 days or symptoms return within 2 weeks after antibiotic treatment A
> Suspect resistant pathogens‡
> Consider CT scan for anatomic considerations
→ Antibiotic treatment B (covers less-susceptible strains of S pneumoniae, H influenzae, M catarrhalis)
→ Antibiotic treatment C (covers less-susceptible strains of S pneumoniae)
ENT CONSULT
• Rule out obstruction, deviated septum, etc
• CT scan
• Antibiotic treatment B for 21 - 28 days
• Anti-anaerobic coverage for chronic infection

Pediatric Sinusitis Treatment Algorithm

Antibiotic treatments:

A Amoxicillin†, TMP-SMX

B Second- and third-generation cephalosporins with adequate *S pneumoniae* coverage (cefprozil, cefuroxime axetil, cefpodoxime proxetil), and amoxicillin-clavulanate†. For penicillin-sensitive patients, macrolides may be considered.

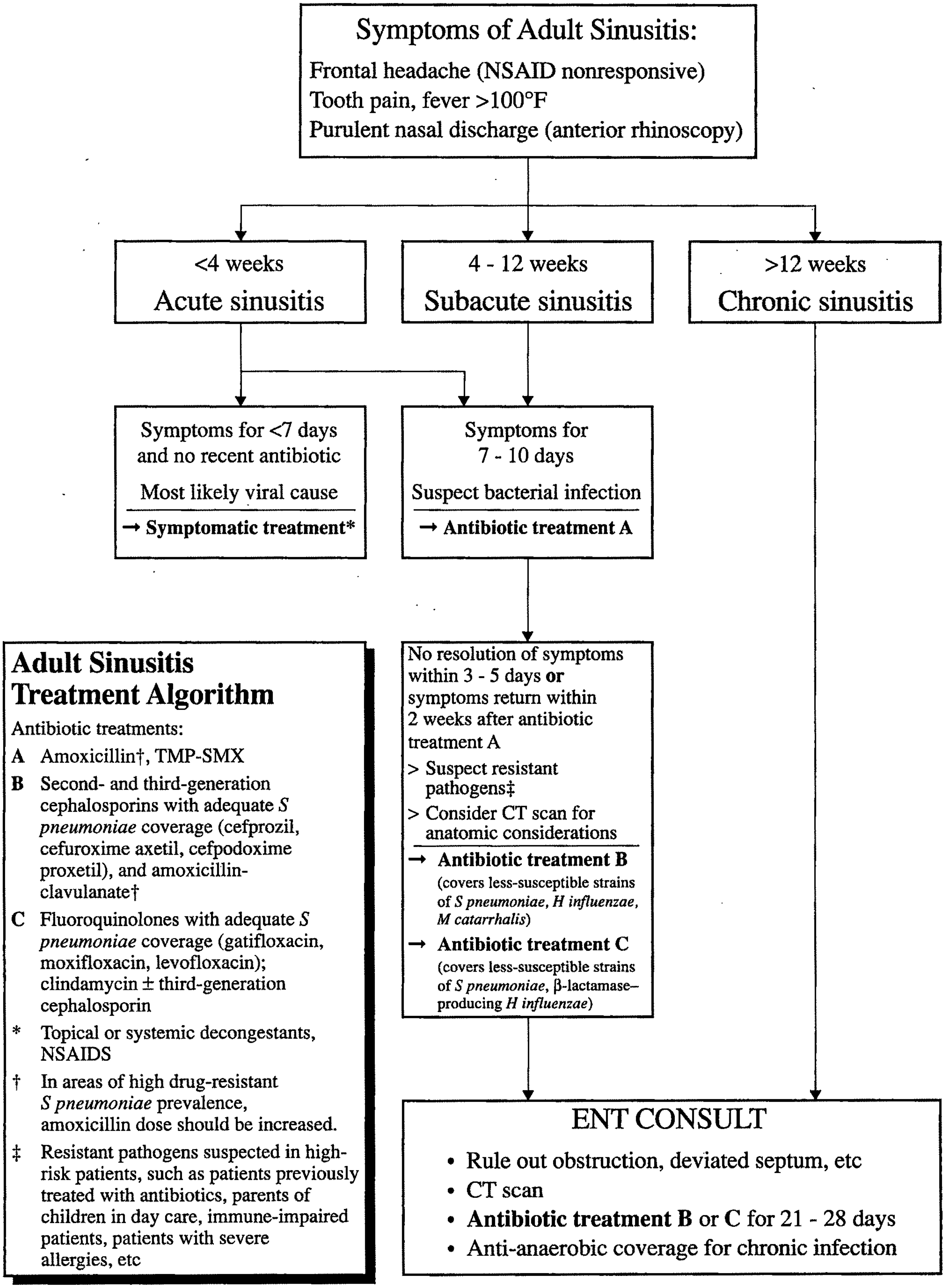
C Ceftriaxone, clindamycin ± third-generation cephalosporin

* Topical or systemic decongestants, NSAIDS

† In areas of high drug-resistant *S pneumoniae* prevalence, amoxicillin dose should be increased.

‡ Resistant pathogens suspected in children in day care, immunity-impaired children, etc

Fig 4. Algorithm for selecting antimicrobial therapy for acute sinusitis in children.


Symptoms of Adult Sinusitis:
Frontal headache (NSAID nonresponsive)
Tooth pain, fever >100°F
Purulent nasal discharge (anterior rhinoscopy)
<4 weeks
Acute sinusitis
4 - 12 weeks
Subacute sinusitis
>12 weeks
Chronic sinusitis
Symptoms for <7 days and no recent antibiotic
Most likely viral cause
→ Symptomatic treatment*
Symptoms for 7 - 10 days
Suspect bacterial infection
→ Antibiotic treatment A
No resolution of symptoms within 3 - 5 days or symptoms return within 2 weeks after antibiotic treatment A
> Suspect resistant pathogens‡
> Consider CT scan for anatomic considerations
→ Antibiotic treatment B (covers less-susceptible strains of S pneumoniae, H influenzae, M catarrhalis)
→ Antibiotic treatment C (covers less-susceptible strains of S pneumoniae, β-lactamase–producing H influenzae)
ENT CONSULT
• Rule out obstruction, deviated septum, etc
• CT scan
• Antibiotic treatment B or C for 21 - 28 days
• Anti-anaerobic coverage for chronic infection

Adult Sinusitis Treatment Algorithm

Antibiotic treatments:

A Amoxicillin†, TMP-SMX

B Second- and third-generation cephalosporins with adequate *S pneumoniae* coverage (cefprozil, cefuroxime axetil, cefpodoxime proxetil), and amoxicillin-clavulanate†

C Fluoroquinolones with adequate *S pneumoniae* coverage (gatifloxacin, moxifloxacin, levofloxacin); clindamycin ± third-generation cephalosporin

* Topical or systemic decongestants, NSAIDS

† In areas of high drug-resistant *S pneumoniae* prevalence, amoxicillin dose should be increased.

‡ Resistant pathogens suspected in high-risk patients, such as patients previously treated with antibiotics, parents of children in day care, immune-impaired patients, patients with severe allergies, etc

Fig 5. Algorithm for selecting antimicrobial therapy for acute sinusitis in adults.

TABLE 8. ANTIMICROBIAL REGIMENS FOR ACUTE SINUSITIS

Antimicrobial Agent	*Dose and Duration*	*Average Wholesale Price Regimen Cost**
Amoxicillin (generic)†	500 mg q12h for 14 d	$8.73
	875 mg q12h for 14 d	$27.13
Amoxicillin-clavulanate (Augmentin)	500 mg/125 mg q8h for 10 d	$106.88
	875 mg/125 mg q12h for 10 d	$95.15
Cefprozil (Cefzil)	250 mg q12h for 10 d	$65.94
	500 mg q12h for 10 d	$130.76
Cefuroxime axetil (Ceftin)	250 mg q12h for 10 d	$81.55
Cefaclor (Ceclor)†	500 mg q12h for 10 d	$77.89
Loracarbef (Lorabid)	400 mg q12h for 10 d	$100.00
Cefixime (Suprax)†	200 mg q12h for 10 d	$74.99
Cefdinir (Omnicef)	300 mg q12h for 10 d or	$70.56
	600 mg q24h for 10 d	$141.12
Trimethoprim-sulfamethoxazole (generic)†	160 mg/800 mg q12h for 10 d	$8.02
Azithromycin (Zithromax)†	500 mg on day 1 and 250 mg on days 2-5 or 500 mg for 3 days	$40.53
Clarithromycin (Biaxin)	500 mg q12h for 14 d	$91.28
Levofloxacin (Levaquin)‡	500 mg q24h for 10 d	$85.34
	500 mg q24h for 14 d	$119.48
Moxifloxacin (Avelox)‡	400 mg q24h for 10 d	$87.12
Gatifloxacin (Tequin)‡	400 mg q24 for 10 d	$70.25

*1999 Redbook. Montvale, NJ: Medical Economics Company, 2000;19(2):15-64.

†Not approved in United States for treatment of sinusitis.

‡Not commonly used to treat community-acquired acute bacterial sinusitis, but may have important role for highly resistant or multidrug-resistant strains.

Antihistamines should not be used routinely in acute bacterial sinusitis. They may dry nasal and sinus secretions and thereby limit mucus clearance from the sinus cavity. Antihistaminic therapy should be considered when there are signs and symptoms that suggest an allergic history. Nasal steroids theoretically alter the inflammatory response in rhinosinusitis and decrease edema and obstruction. These agents are not unequivocally effective and are therefore not routinely recommended in the treatment of acute sinusitis, although they may have some benefits in chronic disease.

ECONOMIC BURDEN

Sinusitis exerts a substantial economic burden on society. It is a serious, debilitating, and costly disease. Sinusitis is associated with high direct health care system costs, including facility usage, professional fees, laboratory and clinical testing costs, medication, surgical costs, socioeconomic costs, and reduced quality of life. In a recent 1-year study, 26.7 million patient visits were attributed to sinusitis and related airway disorders, at a cost of $5.78 billion.[6] Cases in children accounted for 30.6% of the overall costs ($1.77 billion), and adults accounted for 69.4% of the overall costs ($4 billion).

The increasing frequency of penicillin-resistant *S pneumoniae* may increase the rate of treatment failures, greatly increasing treatment costs.[120] Costs of treating sinusitis are also rising because of the increasing prevalence of β-lactamase–producing bacteria. Often, costs are underestimated because indirect and out-of-pocket expenses are not considered (ie, over-the-counter adjunctive treatments). Each year, it is estimated that adults have 12.5 million lost workdays, 58.7 million days of restricted activity, and 20.3 million bed-days because of sinusitis.[6]

Patients who have recurring disease use more health care resources and increase costs. Ober[119] showed a positive correlation between the number of episodes and costs in treating sinusitis. Costs increased from $304 for the first episode to $667 for the second episode to $1,743 for the third episode. Unfortunately, as the number of episodes increased, the choice of antibiotics did not change from amoxicillin. A similar pattern of represcribing amoxicillin after an initial acute otitis media episode was observed.[120] Episode-to-episode pattern changes indicated that amoxicillin was prescribed in 67% of initial cases, 47% of second visits, and 39% of third visits.

The judicious use of a more appropriate second-generation cephalosporin is likely to decrease costs in patients with multiple episodes of sinusitis. The US and Canadian guidelines recommend the use of second-line agents to treat recurring infections.[51] Physicians must consider that less-expensive agents that fail may contribute to the emergence of resistance.

Antibiotic costs represent a small portion (10% to 16%) of the total costs of sinusitis treatment, but the inappropriate selection of antibiotic therapy can significantly increase aggregate health care costs (Table 8).[119] Physicians must determine how families will pay for prescriptions in order to remove barriers that may prevent them from obtaining a drug.[114] Out-of-pocket costs may be a significant barrier to compliance. For children, physicians should consider the amount of antibiotic prescribed versus the weight of the patient. This prevents waste and the potential of using leftover antibiotics for future episodes.[114] Although the cost of second-line antibiotics may be more than that of amoxicillin, the overall cost of failure may outweigh the medication cost. The larger per-episode costs, including revisits, additional clinical and laboratory testing, and professional and emergency room fees, must be considered.

Selecting antimicrobials that are clinically and bacteriologically effective, associated with good compliance, and well tolerated optimizes economic benefit.[121] The palatability of an antimicrobial may be the deciding factor in choice when comparable efficacy exists. Double-blind taste comparisons of pediatric antibiotic suspensions found that the cephalosporins tend to be preferred. Loracarbef, cefadroxil, cefprozil, and cefixime were the 4 highest-ranked antibiotics.[122]

WHEN TO REFER

Improperly treated sinus infections may spread to nearby structures (eye, dura, or venous drainage) through anastomosing veins or by direct extension.[12] Sinusitis is the primary source of infection in two thirds of patients with intracranial abscesses and in 5% of community-acquired bacterial meningitis cases.[12] A patient should be referred to a specialist when a potentially serious complication arises. A referral to an otolaryngologist or an allergist is appropriate when there are recurrent or chronic symptoms, nasal polyposis, asthma, or allergies. Otolaryngologists serve a primary role in the management of complicated and chronic sinusitis.[123] The complications that require a referral to an otolaryngologist include a deteriorating patient condition, treatment failure, immunocompromise, or the development of a nosocomial infection.[80]

Although CT scanning and magnetic resonance imaging have a minor role in the diagnosis of acute bacterial sinusitis, they have a definite role in the management of complicated sinusitis.[94] A CT scan is required to diagnose chronic sinusitis. Computed tomographic scans are superior to plain radiographs in the delineation of sinus abnormalities and have greater sensitivity and specificity.[30,124] In children, CT scanning confirms the most common site of infection to be the ethmoid infundibulum and the anterior ethmoid complex.[125] However, CT scans should be reserved for children with complicated sinus disease, numerous recurrences, or protracted or unresponsive cases in which surgery is contemplated.

A child should be referred for cultures when he or she is severely ill or toxic-appearing, when symptoms progress despite medical management, when he or she is immunocompromised, or when suppurative complications are present.[8] A skilled otolaryngologist should perform the aspiration of the maxillary sinuses. Recovery of bacteria at a density of 10^4 colony-forming units per milliliter represents true infection.[126,127] In addition to the 3 most common pathogens, *S aureus* and anaerobes may be present. Intravenous antibiotics are recommended in severely ill children.

Patients with acute sinusitis rarely require surgical intervention or sinus aspiration to ventilate a sinus that is unresponsive to antimicrobial treatment.[33] Surgery should be considered only when all medical options have been exhausted, and it is generally reserved for patients with refractory disease or anatomic abnormalities. Evaluations by a medical specialist and a surgical specialist may be warranted because of the high complication rate of surgery. Surgery in children may interfere with the development of the face, possibly leading to asymmetrical development.[125] The role of adenotonsillectomy in treating pediatric sinusitis is unclear. Consultation with an otolaryngologist helps determine the size of the tonsils and adenoids, their role in possible sinus obstruction, and the need for their removal.[128]

A referral to an allergist is appropriate when the patient has a significant allergic history. Medical and surgical treatment of sinusitis in patients with asthma reduces the use of asthma medications. This type of referral may be necessary even without complications.[129]

CONCLUSIONS

The literature is full of clinical studies and review articles that deal with sinusitis. Unfortunately, there are few universally accepted guidelines for diagnosis and management. In 1997, the Canadian Sinusitis Symposium developed guidelines for the diagnosis and treatment of sinusitis.[51] Rachelefsky[130] discussed the need for practical national guidelines for the diagnosis and treatment of rhinitis, but there is only minimal mention of sinusitis. The Joint Task

Force on Practice Parameters for Allergy and Immunology has developed guidelines to aid the clinician in decision-making.[111] This comprehensive document covers every major aspect of sinusitis in various formats (Figs 4 and 5).

The optimal management of acute sinusitis is controversial.[6] Primary care physicians must focus on better diagnosis of this condition. A proper diagnosis that focuses on differentiation between viral disease and bacterial infection is required to offer appropriate treatment. This diagnosis can rely largely on patient history and physical examination. Rarely are laboratory tests required. Treatment for sinusitis should focus on relieving the obstruction, treating the infection, thinning the mucus, and opening the sinus ostia.

When a bacterial origin is suspected, an antibiotic should be selected on the basis of resistance patterns found in the community. Regardless of patient pressure, prescribing antibiotics for nonbacterial causes is to be discouraged and replaced with patient education and attention. Appropriate antibiotic selection and duration of use is important to achieve efficacy and prevent antibiotic resistance. Adjunctive treatment may aid in the resolution of signs and symptoms. Patients who do not respond to treatment should be referred to an otolaryngologist to minimize complications. Appreciation of the high incidence of sinusitis and its impact on quality of life should stimulate primary care physicians to properly recognize the subtle clinical presentation of acute bacterial sinusitis and offer appropriate aggressive treatment.

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CONTROVERSIES IN THE MEDICAL MANAGEMENT OF PERSISTENT AND RECURRENT ACUTE OTITIS MEDIA

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OF OTOLOGY,
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LARYNGOLOGY

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Streptococcus pneumoniae is the predominant bacterial pathogen associated with acute otitis media (AOM), causing an estimated 7 million cases annually in the United States. Bacterial resistance should be considered when selecting an antimicrobial agent for otitis media. Significant increases in drug-resistant *S pneumoniae* are documented worldwide, and less than 50% of *S pneumoniae* strains are fully susceptible to penicillin in some regions of the United States. Although amoxicillin is recommended for uncomplicated AOM, treatment guidelines should be flexible and adaptable, taking into consideration local and regional susceptibility patterns, the age of the patient, the frequency of prior infections, and the response to prior therapy. Resistant organisms are more prevalent in children younger than 2 years of age and in those who have recurrent or persistent AOM. Overdiagnosing AOM, selecting inappropriate empiric therapy, or both, leads to overuse and misuse of antibiotics and causes increased drug resistance. This article reviews persistent and recurrent AOM and discusses the pitfalls of diagnosis and the practical limitations of current treatment recommendations.

KEY WORDS — cephalosporin, drug-resistant *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, otitis media, penicillin.

The drug-resistant *Streptococcus pneumoniae* (DRSP) therapeutic working group sponsored by the Centers for Disease Control (CDC) proposed a treatment rationale for acute otitis media (AOM).[1] The DRSP therapeutic working group recommended that amoxicillin remain as first-line treatment in patients with uncomplicated AOM — a recommendation that reflects a widespread consensus of opinion.[2-5] However, the practicality and applicability of the treatment guidelines for patients who fail to respond to amoxicillin or are likely to be infected with penicillin-resistant *S pneumoniae* or β-lactamase–producing pathogens has been questioned[2,4,5]; these are often the patients with persistent and recurrent otitis media.

In this article, we discuss the epidemiology, risk factors, common pathogens, antibiotic resistance patterns, and costs for treatment of AOM. We review important factors to consider in antibiotic selection and suggest reasons for treatment failure (Table 1). After consideration of current treatment guidelines and options, we suggest alternative, practical, clinically focused guidelines for the medical treatment of AOM, and propose strategies for clinical intervention to reduce the incidence of these infections.

OVERVIEW OF PERSISTENT AND RECURRENT AOM

Definitions. Persistent AOM is most commonly defined as the persistence of symptoms and signs of middle ear infection following 1 or 2 courses of antibiotic therapy.[6,7] Recurrent AOM is most commonly defined as 3 or more separate episodes of AOM in a 6-month time span or 4 or more episodes in a 12-month time span.[7]

Epidemiology. Some children experience AOM during the first 6 months of life and are more likely to be otitis-prone.[8] A recent prospective study involving more than 600 mothers and infants enrolled in a health maintenance organization (HMO) in Minneapolis found that 48% of the infants had an episode of AOM or otitis media with effusion (OME) during the first 6 months of life and 20% had 2 or more episodes.[9]

A prospective analysis of AOM that involved approximately 500 children in the Boston area, who were observed for 7 years, showed that the peak incidence of AOM occurred between 6 and 12 months of age. By their first birthday, 62.4% of the infants had 1 or more episodes of AOM and 17.3% had 3 or more

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TABLE 1. FACTORS TO CONSIDER IN ANTIBIOTIC SELECTION

Factors to consider in antibiotic selection
Clinical efficacy
Spectrum of activity
Low risk of adverse events
Cost
Antibiotic resistance
Patient compliance features
Confounding factors
Disassociation of pharmacokinetic and pharmacodynamic predictions and clinical efficacy results
Problems with measurements of antibiotic concentrations in middle ear fluids
Variable absorption of amoxicillin
Variable serum concentrations of drugs
β-Lactamase–producing copathogens

episodes. During the first year, the average number of episodes of AOM was 1.2 per person-year; during the second year, it was 1.1 per person-year; and for the third through sixth years, it was 0.6 to 0.8 per person-year. The rate of AOM declined to 0.4 episode per person-year during the seventh year.[8] A retrospective analysis of new episodes of AOM from a large northern California HMO showed that AOM visits peaked at 1.5 per person-year for infants between 6 and 12 months of age and that their relapse rates were the highest (0.4 visit per person-year).[10] Data from the US National Health Interview Survey (NHIS) indicate that the prevalence rate of recurrent AOM increased from 18.7% in 1981 to 26.9% in 1988.[11] The greatest increase occurred in infants younger than 12 months of age.[11]

Risk Factors. An episode of AOM during the first 6 months of life is a risk factor for recurrent otitis media, possibly because of anatomic, physiological, or immunologic factors.[8] Having a sibling with a history of recurrent otitis media is one of the strongest predictive factors for recurrent otitis media; the risk doubles when other factors are equal.[8] A recent prospective, longitudinal study of twins and triplets shows a strong genetic component in the amount of time with middle ear effusion, episodes of middle ear effusion, and AOM.[12] Parental smoking is significantly ($p < .05$) associated with a child's having more than 1 episode of AOM during the first year of life.[8]

A child born in the fall has a higher risk of recurrent otitis media,[9] possibly because these children spend their vulnerable early months of life during the peak months of exposure to winter respiratory pathogens. The presence of a respiratory tract infection or conjunctivitis (which are usually caused by the same pathogens as otitis media) are often associated with concurrent otitis media.[9] Low birth weight, young gestational age, socioeconomic status, number of siblings, and a familial history of allergies or asthma are not significantly associated with an increased risk of recurrent AOM.[8,9] A higher prevalence of recurrent otitis media may occur among children who are male, white, and affluent, and a lower prevalence may occur in African American, Hispanic, and less affluent children.[11]

Children in day care centers are at higher risk for recurrent AOM.[9,11,13] Between 1981 and 1988, the percentage of children in day care centers increased from 11% to 21% ($p < .001$) and the percentage of infants in day care centers increased from 2.2% to 5.0% ($p < .007$).[11] Day care entry at or before 2 months of age, attendance of 30 or more hours per week, and settings with more than 2 children younger than 2 years of age and a total of 5 or more children are risk factors for AOM.[9] There is a higher rate of recurrent otitis media among children who attend day care centers with more than 4 children than among those who attend smaller day care centers,[11] suggesting that the risk of recurrent AOM appears to increase as the number of contacts with other children increases.[13]

A 1996 meta-analysis of risk factors for AOM showed that breast-feeding for at least 3 months reduces the risk of AOM.[13] Breast-feeding has been significantly associated with decreasing the risk of AOM during the first 3 years of life and recurrent AOM during the first year of life.[8] In the Minneapolis study, breast-feeding decreased the risk of AOM during the first 6 months of life, although the association of exclusive breast-feeding and recurrent otitis media was not statistically significant.[9] The NHIS analysis found no protective effect of breast-feeding on recurrent otitis media.[11]

Common Pathogens. Streptococcus pneumoniae is the predominant bacterial pathogen associated with recurrent AOM[6,14,15]; the CDC estimate that *S pneumoniae* causes 7 million cases of otitis media annually in the United States.[16] The second and third most frequently cultured pathogens are *Haemophilus influenzae* and *Moraxella catarrhalis*, respectively. *Streptococcus pyogenes* causes recurrent AOM in up to 13% of patients, and *Staphylococcus aureus*, in no more than 5%.[6,14,17] Middle ear fluid (MEF) cultures from patients with persistent or recurrent AOM have resulted in no growth of pathogenic bacteria in 30% to 50% of patients[6]; this finding suggests that the signs and symptoms of inflammation may persist even when the infecting bacteria have been eradicated by antibiotics or host defenses.

Antimicrobial Resistance. During the 1980s, *H influenzae* was the pathogen most frequently isolated in persistent AOM following amoxicillin therapy.[5] In the 1990s, significant increases occurred in the proportion of otitis media patients infected with DRSP.[14] Concurrently, these organisms became predominant in persistent and recurrent AOM.[6,7,18,19] A recent study found a 46% rate of penicillin-resistant *S pneumoniae* in patients treated with antibiotics for recurrent AOM, and 33% of these strains were highly resistant.[7] Enrichment of β-lactamase–producing *H influenzae* strains to a prevalence rate higher than 50% also occurs after antibiotic treatment in persistent and recurrent AOM.[7]

Costs of Diagnosis and Treatment. In 1997, approximately 20 million physician office visits in the United States were attributed to otitis media. This represents a decline from 1990, the peak year, when 24 million visits were attributed to otitis media.[20] Otitis media accounts for 9% of all pediatric office visits[21] and 25% of prescriptions written in the United States for children younger than 10 years of age.[22]

The cost of recurrent AOM is substantially higher than that of uncomplicated otitis media (ie, infrequent, isolated episodes). A recent retrospective study analyzed medical costs in a random sample of 119,970 children enrolled in a managed care plan.[10] The direct medical costs for an uncomplicated episode of AOM averaged $131, and the cost for otitis media with at least 1 relapse visit averaged $327.[10] Overall, the direct and indirect costs for an episode of recurrent or relapsed AOM were almost 3 times the costs of an uncomplicated episode.[10] The cost of drugs accounted for a relatively small proportion of the total medical costs. Socioeconomic costs were higher with recurrent otitis media than with uncomplicated otitis media.[10] The typical office visit for uncomplicated AOM resulted in 5.9 hours of lost parental work time, with an average cost of $114. The average cost of parental work loss for relapsed or recurrent otitis media was $404.[10]

Another potential cost attributable to recurrent and persistent otitis media relates to the sequelae associated with otitis media and the efforts to prevent or ameliorate the sequelae. The risk of sequelae developing after otitis media is controversial.[23] Studies of relationships between otitis media early in life and developmental deficits later in life have been inconsistent and contradictory.[23] The limitations of retrospective case control studies and prospective cohort studies have contributed to the uncertainty. A large, multicenter, randomized prospective study in the Pittsburgh area will assess the effects of otitis media and the treatment strategies on speech and language development, cognition, and psychosocial function. Data collection is projected to be complete in late 2001, when the youngest child enrolled is 6 years of age.[23] In the United States, young children with frequent episodes of otitis media are often referred for the surgical placement of tympanostomy tubes because of concerns about the effects of frequent or persistent middle ear effusion on a child's hearing. This procedure results in more than 300,000 operations annually for children younger than 3 years of age, with an estimated cost of $750 million.[23] In one prospective study, 1.8% of infants underwent tympanostomy during the first year of life, and 4.2% during the second year of life.[24] The NHIS reported that 1.3% of children had middle or inner ear surgery in 1981 and 2.4% of children had tympanostomy tubes inserted in 1988. This increase in prevalence parallels the increase in recurrent otitis media, and possibly that of resistant pathogens.[24]

REASONS FOR TREATMENT FAILURE

Uncomplicated AOM has a favorable natural history, regardless of antibiotic therapy.[25] A number of factors are implicated when initial empiric treatment for AOM fails. Therapy could fail because of inadequate dosing of orally administered antibiotic, poor absorption, poor patient compliance, or poor tissue-fluid levels at the site of infection.[26] Brook and Yocum[27] described ways that the presence of β-lactamase–producing colonizers or copathogens may "shield" non–β-lactamase–producing pathogens from β-lactam antibiotics. By producing β-lactamase at the site of infection, the copathogens degrade the antimicrobial and render it ineffective against the target organism.[27] In addition, eradication of normally protective indigenous nasopharyngeal flora, including α-hemolytic streptococci, by antimicrobial therapy may allow potentially pathogenic flora to flourish. Brook and Gober[28] conducted a study of amoxicillin-clavulanate and cefprozil in the treatment of children with AOM. The antimicrobial agents were equally effective, but amoxicillin-clavulanate decreased the number of interfering, nonpathogenic bacteria significantly ($p < .001$) compared with cefprozil. The clinical implications of this evident difference between these second-line agents should be studied further because the suppression of interfering, nonpathogenic organisms may alter the course of otitis media. Disturbing the normal upper airway flora may predispose patients to recurrent otitis media.[19] Treatment failure could be attributed either to the presence of a virus in the MEF that interferes with the bacteriologic and clinical response to the antimicrobial agent[29] or to reinfection with the initial organism or a new pathogen.[30]

Patient Compliance. Another important factor to consider is patient compliance. Hoppe and Wahren-

TABLE 2. VALUE OF HISTORY FEATURES, EXAMINATION TECHNIQUES, AND LABORATORY TESTS IN ESTABLISHING DIAGNOSIS OF PERSISTENT AND RECURRENT AOM

	Value
History features	
Age	Valuable
Day care	Valuable
History of acute otitis media (number/duration of episodes)	Valuable
Antibiotics within 1 month	Valuable
Household smoker	Valuable
Symptoms persisting >48 hours	Of variable value
Hearing loss	Valuable
Examination techniques	
Pneumatic otoscopy	Valuable
Tympanometry	Of variable value
Acoustic reflectometry	Of variable value
Laboratory tests	
Tympanocentesis and culture of middle ear fluid	Valuable
OtoLAM laser*	Of variable value

*Alternative to pressure equalization tubes and alternative procedure for tympanocentesis.

berger[31] have studied approximately 300 pediatric patients with AOM and other infections who were prescribed a variety of antibiotic suspensions. Overall, 20% of patients were noncompliant with their treatment. Good compliance was significantly ($p < .05$) correlated with a patient 3 years of age or older.[31] Other factors that affect compliance and treatment efficacy include the tolerability of the treatment and the frequency of drug administration.[32]

STRATEGIES FOR IMPROVING DIAGNOSIS OF PERSISTENT AND RECURRENT AOM

An intriguing finding of the NHIS was that the prevalence of recurrent otitis media was higher among affluent white children who had regular access to medical care than among African American, Hispanic, or less affluent children.[24] The authors postulated that the lower prevalence of recurrent otitis media among disadvantaged children might reflect underdiagnosis in those with less access to medical care.[24] However, another way to interpret the data would be to question whether regular access to medical care predisposes affluent children to an overdiagnosis of AOM. Improving the diagnostic accuracy of AOM could reduce overall antibiotic exposure and the likelihood of developing resistant pathogens and persistent and recurrent otitis media.[33]

For primary care physicians, the difficulty of accurately making an office diagnosis of AOM often leads to overdiagnosis.[13,34] Table 2[35-41] lists some frequently used history features, examination techniques, and laboratory tests and their value in establishing a diagnosis. Many clinicians rely heavily on history and symptoms in making the diagnosis of AOM, even though these are not sufficiently sensitive or specific.

TABLE 3. HISTORY AND PHYSICAL EXAMINATION FEATURES PROVIDING CLUES TO ETIOLOGY OF PERSISTENT AND RECURRENT AOM

More likely to be *Streptococcus pneumoniae* if:
- Increased otalgia and fever
- Spontaneous perforation

More likely to be resistant *S pneumoniae* if:
- Therapy in preceding month was with
  - Erythromycin-sulfisoxazole
  - Trimethoprim-sulfamethoxazole
  - Azithromycin
  - Ampicillin
  - Antibiotic prophylaxis
- Epidemiologic features
  - Younger than 2 years of age
  - Day care
  - History of recurrent acute otitis media
  - Contact with individuals treated with antibiotics

Less likely to be *S pneumoniae* if:
- Mild symptoms
- Preceding therapy was with high-dose amoxicillin

More likely to be *Haemophilus influenzae* if:
- Otitis-conjunctivitis syndrome

More likely to be β-lactamase–positive *H influenzae* if:
- Preceding therapy was with amoxicillin

Less likely to be *H influenzae* if:
- Preceding therapy was with third-generation cephalosporin

Failing to remove ear wax, using an otoscope that provides inadequate light, or using an inappropriately sized speculum will impair visualization of the tympanic membrane.[33,34,42] Pneumatic otoscopy is an examination technique used to facilitate diagnosing AOM through an assessment of the tympanic membrane position and mobility (Table 2). A recently published survey found that 46% of family practitioners and 25% of pediatricians do not routinely perform pneumatic otoscopy.[43] These clinicians may be relying on the red color of the tympanic membrane as a prime diagnostic clue, even though it has been shown that crying and screaming causes the tympanic membrane to become red, so that its diagnostic value is limited. Tympanometry and acoustic reflectometry are also helpful in diagnosis and follow-up.[41]

Tympanocentesis with a culture of the MEF may be useful if the child is clearly in pain, toxic, or has a high fever. The DRSP therapeutic working group stated that diagnostic tympanocentesis might be necessary to guide the choice of therapy in persistent or recurrent AOM. The group recommended that clinicians learn the skills required to perform tympanocentesis or refer the patient to someone who can per-

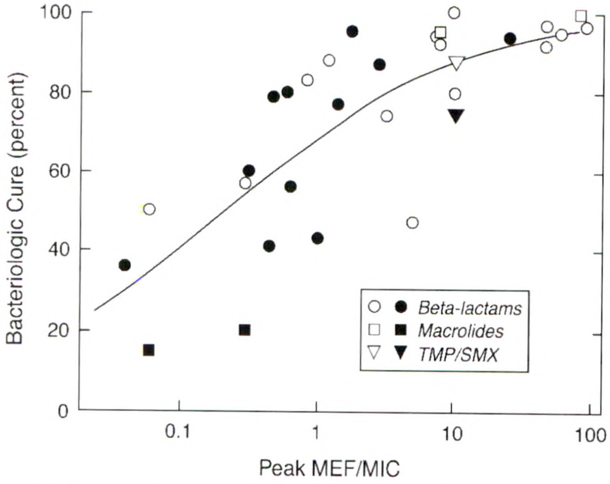

Fig 1. Relationship between peak middle ear fluid:minimum inhibitory concentration ratio (MEF/MIC) and percent of bacteriologic cure. Open symbols — *Streptococcus pneumoniae*; closed symbols — *Haemophilus influenzae* β-lactamase–positive and –negative; *TMP/SMX* — trimethoprim-sulfamethoxazole. (Reprinted with permission.[52])

form the procedure.[1] Evacuation (drainage) of the middle ear effusion can be beneficial in breaking the cycle of persistent and recurrent AOM.[44] The information provided by the culture and susceptibility report may be valuable for treating persistent and recurrent AOM. If a bacterial pathogen is reported, selecting an appropriate antibiotic will reduce the likelihood of further treatment failure; if no bacterial pathogen is isolated, the patient will not require further antibiotic treatment.[6,45] For patients with persistent and recurrent AOM in whom MEF cultures are not available, analyzing previous treatment and current symptoms may give clues to the likely pathogen (Table 3[46-50]).

ANTIMICROBIAL CONSIDERATIONS FOR IMPROVING TREATMENT OF PERSISTENT AND RECURRENT AOM

Bactericidal Concentrations. When selecting an antimicrobial agent for a particular infection, one of the key questions to ask is, "Does the drug achieve and maintain sufficient concentrations at the site of infection to kill the relevant pathogens?" Different types of antimicrobials display different patterns of bactericidal activity. For example, aminoglycosides and fluoroquinolones are concentration-dependent antibiotics; the higher the drug concentration, the greater the rate and extent of bactericidal activity. This is demonstrated by bacterial time-kill curves that illustrate a more rapid, extensive degree of bacterial killing with multiples of the minimum inhibitory concentration (MIC). Hence, the time-kill curve is typically much steeper with a fluoroquinolone than with a β-lactam, which shows only a slight reduction in bacterial counts at higher multiples of MIC. Other classes of antimicrobials, including the β-lactams, follow a different pattern of killing, with maximum bactericidal activity occurring at low multiples of the MIC. The extent of bacterial killing for these agents depends on the time of bacterial exposure to sufficient concentrations of the agent.[51] Most of the antimicrobial drugs used for the treatment of otitis media follow the pattern of time-dependent bacterial killing. Studies of agents in neutropenic mice that follow time-dependent killing have shown that maximal killing occurs when antibiotic serum concentrations exceed the MIC for 40% to 50% of the time between doses.

TABLE 4. LIKELIHOOD OF CLINICAL SUCCESS IN TREATING AOM BASED ON PHARMACOKINETIC AND PHARMACODYNAMIC DATA

	Streptococcus pneumoniae*			Haemophilus influenzae	
Antibiotic	*S*	*I*	*R*	*β-Lactamase –Negative*	*β-Lactamase –Positive*
Amoxicillin 80-100 mg/kg per day	5	5	4	5	1
Amoxicillin 40-50 mg/kg per day	5	4	3	5	1
Amoxicillin-clavulanate	5	4	3	5	5
Cefaclor	5	3	2	5	3
Cefprozil	5	4	3	5	4
Loracarbef	5	3	2	5	3
Cefuroxime axetil	5	4	3	5	4
Cefixime	5	2	1	5	5
Cefpodoxime proxetil	5	4	3	5	5
Ceftibuten	5	2	1	5	5
Cefdinir	5	3	1	5	5
Ceftriaxone sodium†	5	5	4	5	5
Clarithromycin	5	3	2	3	3
Azithromycin	5	3	2	3	3
Trimethoprim-sulfamethoxazole	5	3	2	3	3
Erythromycin-sulfisoxazole	4	3	1	3	3

Antibiotics rated on ordinal scale from 1 (least likely to be effective) to 5 (most likely to be effective).

**Streptococcus pneumoniae* susceptibility to penicillin: susceptible (S), intermediately resistant (I), or resistant (R).

†Ceftriaxone sodium efficacy against intermediately resistant and resistant *S pneumoniae* has been optimal when administered as 3 injections on 3 consecutive days.

In the context of bacterial otitis media, MEF concentrations are often used to predict efficacy. The ratio of the MEF concentration of the antimicrobial agent to the MIC of the otitis media pathogen is used to predict bacterial eradication. Craig and Andes[52] have reviewed and compiled published data from studies of MEF and serum concentrations of antimicrobials. From nonlinear regression analysis, an

MEF:MIC ratio of between 3.2 and 6.3 would correlate with 80% to 85% antibacterial efficacy, and a ratio greater than 10 would predict maximum efficacy (Fig 1[52]).

Middle Ear Fluid–Minimum Inhibitory Concentration Model. The MEF:MIC model is useful in selecting antimicrobial agents and designing dosing regimens for AOM (Table 4[1,18,25,26,53-71]). However, relying too heavily on the concept may lead to the selection of a suboptimal antimicrobial regimen, because insufficient human data are available for most antimicrobials to characterize the entire concentration-versus-time profile in MEF.[52] The differences in study design, patient population, drug assays, and other factors complicate the interpretation of the available results.[52] Most of the data are from studies that used a nonrandomized design, a small sample size, and patients scheduled to undergo surgical procedures, who had chronic otitis media rather than AOM. Administering oral antimicrobials to patients who fasted to prepare for surgery may not reflect real-life conditions for drug absorption. Only very small amounts of MEF are available for antibiotic concentration sampling, and using small amounts can cause errors in high-pressure liquid chromatography assays of drug levels. There is considerable potential for contaminating MEF samples with peripheral blood cells and serum. The presence of serum and cells in the MEF may affect the measurement of antimicrobial concentrations. For example, Scaglione et al[72] recently performed a randomized study using tympanocentesis to obtain MEF samples from patients with AOM. They found that the MEF concentrations of drugs were influenced by concurrent serum concentrations and that the cell content of the MEF affected the measurable antibiotic concentrations. Cephalosporin concentrations were negatively affected and azithromycin concentrations were positively affected by the presence of cells in the fluid.[72]

Practical Issues Related to DRSP Therapeutic Working Group Recommendations. The DRSP therapeutic working group relied on MEF concentration data when formulating their recommendations.[1] In addition to the methodological problems previously discussed, significant interindividual variations in the absorption of amoxicillin may lead to significant interpatient variability in "achievable" MEF concentrations (Table 4).[73]

Amoxicillin is absorbed in the duodenum and jejunum.[73] Dose-dependent oral bioavailability for amoxicillin has been demonstrated in human subjects[74,75] and absorption of amoxicillin is not entirely dependent on passive diffusion kinetics. Investigators have demonstrated variable, nonlinear absorption kinetics attributable to a saturable carrier-mediated uptake and simple diffusion.[76,77] In a patient who has poor absorption kinetics, double-dosing amoxicillin does not overcome the variability in absorption that is due to the saturable uptake of amoxicillin.

Amoxicillin-clavulanate is a drug proven to be efficacious in AOM.[1] The DRSP therapeutic working group recommended a formulation of amoxicillin-clavulanate that is not available in the United States.[1] To provide the recommended ratio of amoxicillin to clavulanate would require prescribing the current formulation plus added amoxicillin. Parents would have to fill two separate prescriptions and follow two separate dosing schedules — a regimen that can be confusing and undermine patient compliance. Also, persistence of AOM or an early recurrence may be due to β-lactamase–producing pathogens, copathogens, poor absorption, or other patient-specific factors. Switching from amoxicillin to amoxicillin-clavulanate solves some, but not all, of these issues.[4]

The DRSP therapeutic working group recommended intramuscular ceftriaxone sodium for patients with persistent and recurrent AOM.[1] Ceftriaxone has been proven efficacious; however, the optimum duration of therapy with ceftriaxone for these patients has not been determined.[65] Several clinical trials show that a single 50-mg/kg intramuscular injection of ceftriaxone is effective in children with uncomplicated AOM.[53,56] It is often a good choice if a patient is vomiting, has diarrhea, refuses all oral medications, or is toxic. The only published clinical trials of ceftriaxone for the treatment of persistent and recurrent AOM have administered 3 consecutive daily injections of ceftriaxone.[58,65] The DRSP therapeutic working group stated that 3 consecutive daily injections might be needed for persistent and recurrent AOM.[1] A 3-day regimen would require 3 separate office visits and increase direct and indirect costs. Three intramuscular injections of ceftriaxone may not be well accepted by the patient.

The oral cephalosporin of choice selected by the DRSP therapeutic working group was a second-generation cephalosporin: cefuroxime axetil. A second-generation cephalosporin was considered most ideal, because of the balance in gram-positive (*S pneumoniae*) and gram-negative (*H influenzae* and *M catarrhalis*) bactericidal activity. At the time of the working group review, cefuroxime was the most widely studied agent with the overall best results in the MEF:MIC model and in clinical trials. The major practical challenge with cefuroxime is the taste and aftertaste problem of the liquid form of the agent. The reduction in patient compliance can be overcome in some children by disguising the taste with chocolate syrup, ice cream, pudding, or a white grape juice chaser. However, some children simply refuse to take this antibiotic.

Clindamycin was also cited as a possible choice for persistent and recurrent AOM.[1] However, because clindamycin is ineffective against *H influenzae* and *M catarrhalis*, it cannot be an empiric choice and only becomes acceptable after tympanocentesis confirms that the pathogen is *S pneumoniae*.

The DRSP therapeutic working group also reported that it considered cefprozil and cefpodoxime proxetil as alternative treatments for persistent and recurrent otitis media. At the time of their review of the data, the working group did not recommend either of these agents, because they believed that there was "limited evidence" of efficacy against DRSP in clinical trials.[1] However, they did note the promising results of an open-label trial of cefprozil in persistent and recurrent AOM in which cefprozil-treated patients who were infected with *S pneumoniae*, *H influenzae*, or *M catarrhalis* achieved satisfactory clinical results.[7] Cefdinir was not licensed at the time the DRSP group reviewed available agents.

A PRACTICAL APPROACH TO ANTIBIOTIC RECOMMENDATIONS

Klein[4] outlined a practical approach to selecting agents for use after amoxicillin failure. His approach is based upon the local prevalence of penicillin-resistant *S pneumoniae*. In areas with lower rates of penicillin-resistant *S pneumoniae* (<20%), β-lactamase–producing pathogens may be selected more often after amoxicillin failure, suggesting the use of β-lactam or non–β-lactam antimicrobial agents with better gram-negative coverage. If therapy with a β-lactam agent fails, a non–β-lactam agent should be selected for third-line therapy. In areas with higher rates of penicillin-resistant *S pneumoniae* (≥20%), a strategy of using β-lactam and non–β-lactam agents with better antipneumococcal activity should be followed.[4,5] Aronovitz[2] recommended that clinicians develop a personal treatment armamentarium that consists of a manageable number of antibiotics for first-line, second-line, and third-line use.

Despite some of the practical limitations of the DRSP working group's recommendations, they have considerable merit. Starting with standard- or high-dose therapy using amoxicillin for uncomplicated AOM is reasonable, especially when one considers the frequency of overdiagnosis of AOM and the high spontaneous cure rate of this condition. Deciding to continue or switch therapy on the basis of the clinical response on the third day gives the selected antibiotics enough time to work or fail. Including traditional second-line antibiotics as first-line choices if the patient has already been on an antibiotic within the previous month is an idea whose time has come in an era of rising bacterial resistance.[45] The introduction of tympanocentesis as a diagnostic and therapeutic tool is a laudable goal that should be pursued.[45] A follow-up examination should be performed, usually 3 to 4 weeks after diagnosis unless symptoms recur, to avoid missing an indolent, persisting infection. The selection of amoxicillin-clavulanate, cefuroxime, and ceftriaxone as second-line agents for persistent and recurrent AOM is appropriate, because the logic is sound and the evidence is reasonable. However, clinicians should be guided by the considerations previously discussed when selecting a second-line agent. Cefprozil, cefpodoxime, and possibly cefdinir should be added to this list of choices, with careful evaluation of new clinical trial results that emerge regarding these agents and newer ones (Fig 2).

CURRENT AND FUTURE STRATEGIES FOR CLINICAL INTERVENTION

One of the key recommendations of the DRSP therapeutic working group is the use of high-dose oral amoxicillin-clavulanate in a formulation that has not been approved for use in the United States.[1] The dosage of the current formulation of amoxicillin-clavulanate for infants and children weighing less than 40 kg who have otitis media is based on an amoxicillin dose of 40 mg/kg per day. A new formulation is being evaluated that provides the two components at a ratio such that amoxicillin is given at 90 mg/kg per day and clavulanate is given at 6.4 mg/kg per day. A multicenter, randomized study in the United States compared this formulation and one of amoxicillin at 45 mg/kg per day and clavulanate at 6.4 mg/kg per day, each given in 2 divided doses with food for 10 days in 411 children with AOM. The clinical results in the two treatment groups were statistically equivalent, with 84.1% of the high-dose group and 78.8% of the low-dose group achieving clinical cure with no recurrence at follow-up. Diarrhea was noted in both treatment groups, but there was no statistically significant difference between the two groups in the prevalence of diarrhea or other adverse events.[78]

A new conjugate heptavalent pneumococcal vaccine is another promising approach to reducing the magnitude of the problem of persistent and recurrent AOM. The principal disadvantage of the unconjugated vaccines is that many of the 23 pathogenic pneumococcal serotypes included in the vaccine are not effective inducers of a protective antibody response in children younger than 2 years of age. The poor immunogenicity is due to a T-cell–independent

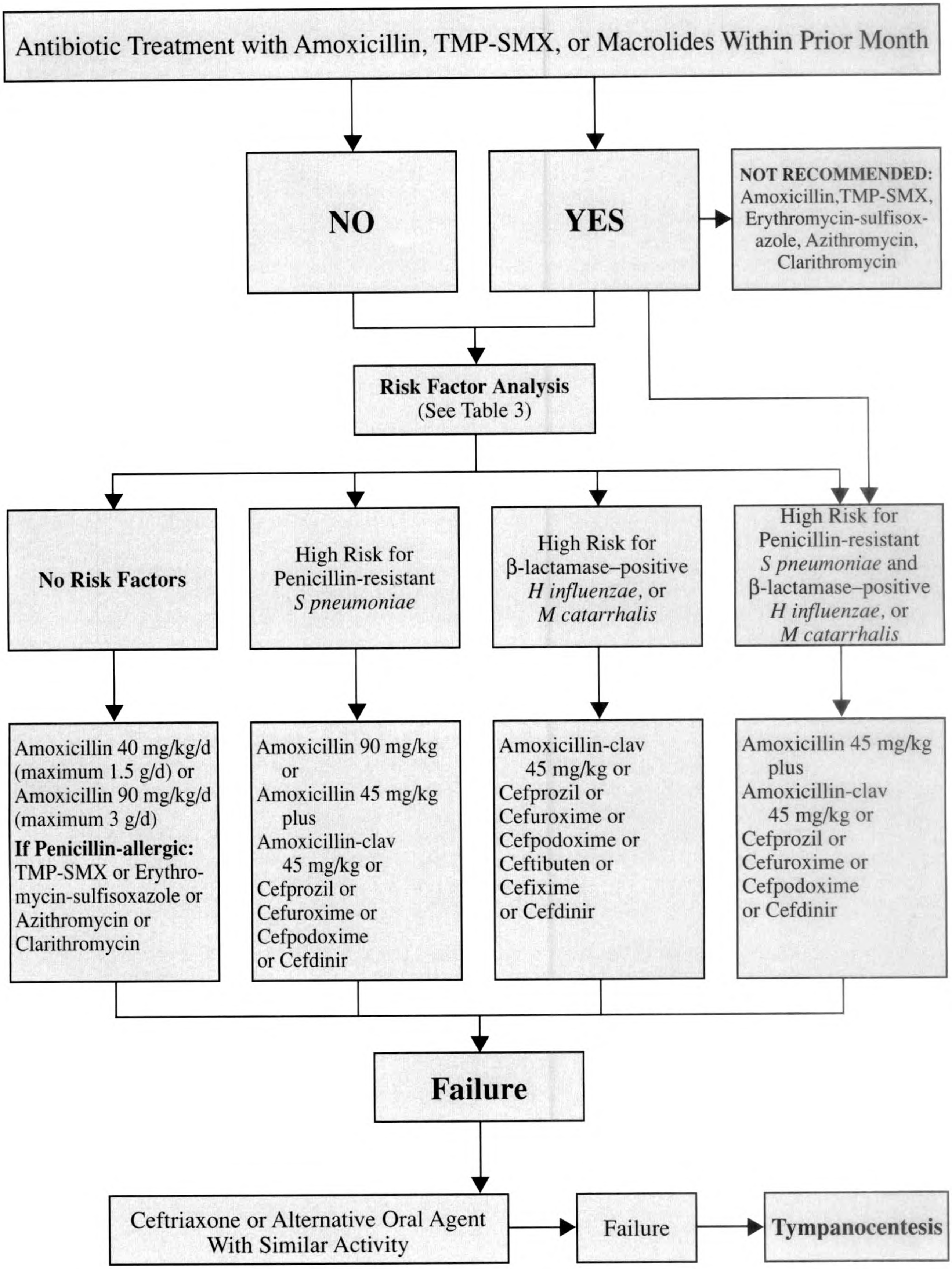
Antibiotic Treatment with Amoxicillin, TMP-SMX, or Macrolides Within Prior Month
NO
YES
NOT RECOMMENDED: Amoxicillin,TMP-SMX, Erythromycin-sulfisoxazole, Azithromycin, Clarithromycin
Risk Factor Analysis (See Table 3)
No Risk Factors
High Risk for Penicillin-resistant S pneumoniae
High Risk for β-lactamase–positive H influenzae, or M catarrhalis
High Risk for Penicillin-resistant S pneumoniae and β-lactamase–positive H influenzae, or M catarrhalis
Amoxicillin 40 mg/kg/d (maximum 1.5 g/d) or Amoxicillin 90 mg/kg/d (maximum 3 g/d) If Penicillin-allergic: TMP-SMX or Erythromycin-sulfisoxazole or Azithromycin or Clarithromycin
Amoxicillin 90 mg/kg or Amoxicillin 45 mg/kg plus Amoxicillin-clav 45 mg/kg or Cefprozil or Cefuroxime or Cefpodoxime or Cefdinir
Amoxicillin-clav 45 mg/kg or Cefprozil or Cefuroxime or Cefpodoxime or Ceftibuten or Cefixime or Cefdinir
Amoxicillin 45 mg/kg plus Amoxicillin-clav 45 mg/kg or Cefprozil or Cefuroxime or Cefpodoxime or Cefdinir
Failure
Ceftriaxone or Alternative Oral Agent With Similar Activity
Failure
Tympanocentesis

Fig 2. Algorithm for treatment of acute otitis media.

immunogenic response. The conjugate heptavalent vaccine contains polysaccharides of pneumococcal serotypes 4, 6B, 9V, 12, 19F, and 23F, and the oligosaccharide of serotype 18C conjugated to a nontoxic variant of the diphtheria toxin. The vaccine is safe and immunogenic when administered at 2, 4, and 6 months of age with a booster between 12 and 15 months of age.[79,80] In a study conducted at a large HMO in northern California, vaccinated children had significantly lower ($p < .05$) incidences of physician visits for otitis (8.9%), episodes of otitis (6.4%), frequent otitis (9.3%), and tympanostomy tube placement (20.1%).[81]

Although 10 days of antimicrobial therapy for AOM has been traditionally advocated in North America, there currently is a growing interest in shorter courses of treatment. Comparative trials of shorter and longer courses of antibiotics have recently been the subject of a comprehensive review[82] and a meta-analysis.[83] The authors concluded that shortened courses of antibiotics were likely to be successful for most patients older than 2 years of age with uncomplicated AOM. Subsequently, other shortened courses of therapy for AOM have followed and shown favorable results.[84]

Currently, there is insufficient evidence from randomized trials to make an across-the-board recommendation for shorter treatment courses for patients younger than 2 years of age. Children younger than 2 years of age have the highest incidence of first episodes of AOM and persistent and recurrent otitis media.[8,10,11] Resistant pathogens are most likely to be found among patients in this age group.[17]

For children older than 2 years of age and those with uncomplicated AOM, the potential benefits of shorter courses of antibiotic treatment could be considerable. For both the patient and the parent, shorter courses of treatment would be more acceptable, promote improved compliance, and may result in reduced incidence and severity of adverse events. Shorter courses of treatment also would reduce overall antibiotic exposure and might help to slow the development and spread of resistant pathogens.

CONCLUSION

Overdiagnosis of AOM is frequent and leads to overuse and misuse of antibiotics and increased antibiotic resistance. The incidence of persistent and recurrent AOM may be reduced through more accurate diagnosis, appropriate selection of antimicrobial agents for empiric treatment, and more practically designed (short versus long) treatment regimens.

Selecting antimicrobial agents for treating AOM often relies too heavily on in vitro data and comparisons of concentrations in the MEF; other factors, including clinical efficacy, potential risk of adverse events, and likelihood of compliance should be considered. It is important to keep apprised of the local and regional susceptibility patterns of the most common pathogens and to factor this information into the choice of empiric treatment regimens.

There is a need for further discussion of a set of practical, evidence-based treatment guidelines for persistent and recurrent otitis media that will be used by primary caregivers and specialists. These treatment guidelines should be flexible and adaptable.

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24-HOUR AMBULATORY pH MONITORING FOR PATIENTS WITH SUSPECTED EXTRAESOPHAGEAL COMPLICATIONS OF GASTROESOPHAGEAL REFLUX: INDICATIONS AND INTERPRETATIONS

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OF OTOLOGY,
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24-HOUR AMBULATORY PH MONITORING FOR PATIENTS WITH SUSPECTED EXTRAESOPHAGEAL COMPLICATIONS OF GASTROESOPHAGEAL REFLUX: INDICATIONS AND INTERPRETATIONS

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INTRODUCTION

The diagnosis of extraesophageal reflux (EER) is evasive, and yet the effects of the disorder are far-reaching. These reports, representing a panel presentation of the 1999 meeting of the American Broncho-Esophagological Association, are intended to promote a consensus on terminology, diagnosis, and management. The term "extraesophageal reflux" appears to be the most all-inclusive one that could be used to describe areas of involvement with gastroesophageal reflux (GER) to include 1) the direct refluxate and 2) neurogenic stimulation to the areas of the larynx, pharynx, and tracheobronchial tree. Although there is widespread use of the terms "supraesophageal complications of reflux disease"[1] and "laryngopharyngeal reflux,"[2] the panel agreed that these terms ignored the tracheobronchial tree.

Although 2-site probe testing in the upper and lower esophagus appears sufficient in the pediatric population, the addition of a pharyngeal probe in adults appears to be vital. There is a need in all situations to have a lower esophageal probe to prove the validity of a reflux event. Placement of the upper probe 1 to 2 cm above the cricopharyngeus muscle is standard, but requires time and skill with manometric control. The "Amsterdam" method, in which the upper probe is placed in the upper esophageal sphincter at the level of the cricopharyngeus muscle endoscopically, may prove to be very effective in diagnosing laryngopharyngeal reflux.[3] In addition, it provides the added information that can be obtained by endoscopy of this area.

A drop in pH to levels of 4 or below in the pharynx or upper esophagus is considered diagnostic of a reflux event. A single reflux event in the pharynx is likely diagnostic of EER, although some "normals" have been found to have pharyngeal reflux events.[4] There is some suggestion that a pH of 4 or below is too rigid a criterion and that further studies of events at pH 5 or even above 5 might show them to be indicative of EER (see Postma, this supplement, pp 10-14).

There is consensus that patients with EER should undergo a trial of acid suppression therapy before a probe study is recommended. If this conservative approach fails even with high dosages of H2 or proton pump inhibitor medication, a probe study will be helpful in planning further treatment, especially if fundoplication is to be done. The problem patient who cannot or will not tolerate a probe study can be evaluated endoscopically (see Aviv et al, this supplement, pp 25-27). The exception to this delayed use of a probe study would be patients with life-threatening disorders such as laryngospasm and laryngotracheal stenosis. In these cases, early probe study is essential to mapping out further early treatment.

The limitations of the probe study are significant. Overall, the sensitivity of the study is no more than 75% to 80%.[5] Although the method remains the "gold standard" for documenting EER, it does not give significant information as to neurogenic mechanisms of EER. There are studies that indicate that neurogenic EER may be at least as significant as direct reflux events to the upper esophagus and pharynx.[6,7] Further limitations include the invasiveness, time, and expense of probe study.

These papers are the "state of the art" in terms of information for the practitioner. The overview, methods, adult and pediatric indications, and alternative measures for 24-hour ambulatory pH monitoring for patients with suspected EER complications of GER are presented in detail. It is obvious that more precise, less costly, and less invasive methods are needed, and future investigations will certainly be forthcoming. We must expand our knowledge, diagnosis, and treatment of this very contemporary and challenging part of otolaryngology–head and neck surgery.

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ROLE OF ESOPHAGEAL PH RECORDING IN MANAGEMENT OF CHRONIC LARYNGITIS: AN OVERVIEW

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Chronic laryngitis typically produces symptoms of frequent throat-clearing, soreness, decreased voice quality with use, nonproductive cough, globus sensation, and odynophagia. The endoscopic laryngeal examination usually demonstrates posterior glottic edema, erythema, and increased vascularity and nodularity. There is increasing support for the hypothesis that reflux of acidic gastric contents is often responsible for the symptoms and findings of chronic laryngitis. Prospective trials of acid suppression therapy demonstrate not only efficacy in symptom reduction, but also objective improvement in measurements of voice quality and mucosal erythema. Although traditionally considered the "gold standard" for diagnosis of reflux causing laryngitis, routine esophageal pH recording may result in false negatives in up to 50% of patients. This may confound the diagnosis of chronic laryngitis and delay treatment. Conversely, a positive study during comprehensive therapy may help identify patients who need additional treatment. A single distal probe is probably insufficient for evaluation of a supraesophageal disorder. Current recommendations for double-probe pH study in the evaluation of chronic laryngitis fall into 2 categories: 1) a double-probe pH study is indicated if there is ongoing moderate-to-severe laryngitis despite antireflux precautions and proton pump inhibitor treatment for at least 6 to 12 weeks; and 2) a double-probe pH study is indicated as a baseline measurement before Nissen or Toupet fundoplication. The pH study would also be indicated in patients who have symptoms after fundoplication. There is clearly much more work to be done on the technical issues of obtaining accurate objective data related to laryngeal acidification. In addition, although acid reflux appears to be causative in many cases of chronic laryngitis, further work is indicated to identify reliable testing methods that will predict treatment success.

KEY WORDS — chronic laryngitis, esophageal pH probe study, gastroesophageal reflux.

INTRODUCTION

Frequent throat-clearing, soreness or irritation of the throat, hoarseness or deterioration of voice quality with use, nonproductive cough, globus sensation, and odynophagia — all symptoms of chronic laryngitis — are symptoms that today are likely to motivate a referral to an otolaryngologist.[1-6] With better methods of visualizing the hypopharynx and larynx, chronic laryngitis symptoms can be associated with typical signs: posterior glottic edema, erythema of the epithelium, increased vascularity of the mucosal surfaces, nodularity or granular appearance, granuloma, and contact ulceration.[2,4,6] Although Cherry and Margulies[7] years ago implicated gastropharyngeal reflux of gastric juices as a likely factor in the formation of contact ulcers of the larynx, it was only relatively recently that a growing body of clinical evidence supported the notion that reflux of gastric fluids into the hypopharynx is probably an important factor in the causation of chronic laryngeal inflammation as well as of contact ulcers.[1-6] Chronic laryngeal inflammation from this source may even be a factor in the development of cancer.[8,9] It has been shown that gastric acid can cause the kinds of tissue injury that are seen with chronic laryngitis.[10,11] However, there has not been definitive proof that reflux of gastric acid is the causative agent of the changes that we see with typical chronic laryngitis.

CLINICAL STUDIES WITH ACID SUPPRESSION

With the introduction of potent proton pump inhibiting agents that profoundly suppress gastric acid secretion, it became feasible to test the hypothesis that acid reflux might be an important factor in the cause of chronic laryngitis. In 1994, Kamel et al[3] reported a prospective study of patients with chronic laryngitis symptoms and signs who were treated with a proton pump inhibitor. After entry to the study, patients were asked to record the symptoms that they experienced on a daily basis during a trial of treatment with a proton pump inhibitor (40 mg/d) along with a concerted effort to take precautions against gastropharyngeal reflux during sleep. Videolaryngoscopic examination and voice recordings were performed at regular intervals during treatment. That study showed that laryngeal symptoms as well as esophageal symptoms resolved with acid suppression treatment and that symptoms returned when treatment was discon-

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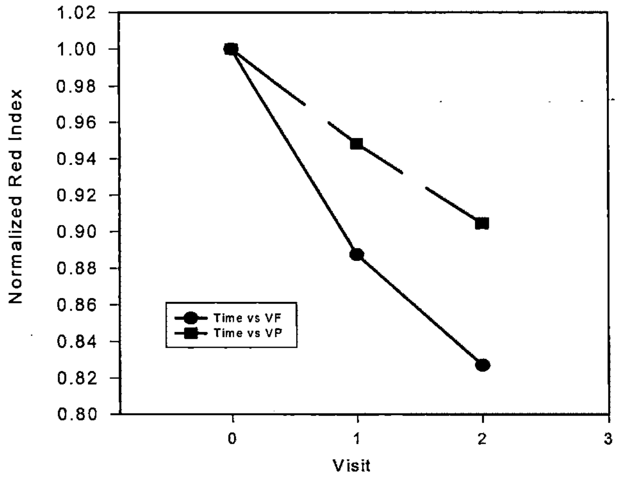

Fig 1. Visit versus normalized red index (patient T).

tinued. In addition, documented laryngoscopic findings of the patients were judged to measurably change (improve) with treatment.[3]

One of the indications of laryngitis that seemed to respond to antireflux treatment in that prospective study was erythema of the mucous membranes.[3] Subsequent analyses of laryngoscopic examinations have been made with use of software that allowed quantitative measurement of the value of red in digitized laryngeal images. The value of red was calibrated to the overall color value of red + blue + green. Measurement of the red color value on the vocal folds and the posterior mucosal surface over the corniculate cartilages showed a significant difference between patients with chronic laryngeal symptoms and subjects with normal larynges and no laryngopharyngeal complaints.

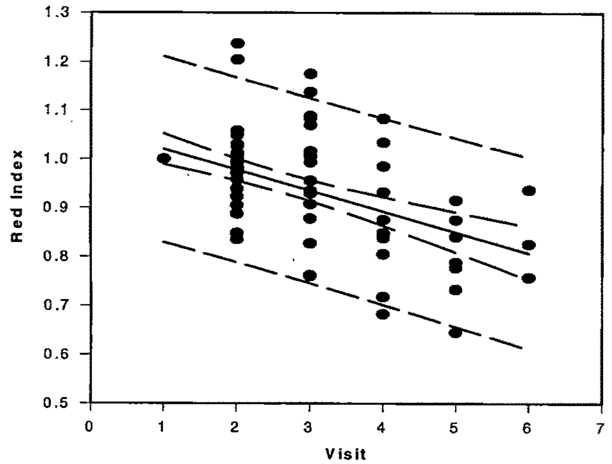

Fig 2. Group data during treatment.

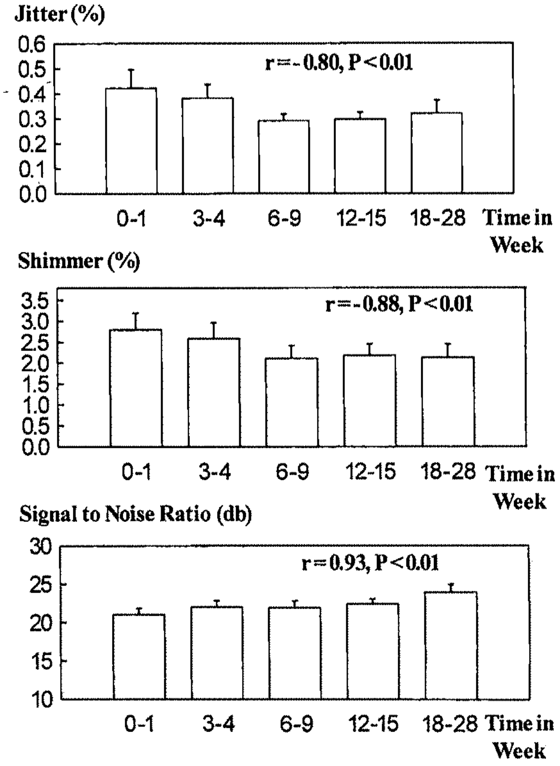

Fig 3. Data for acoustic measures during treatment (from Hanson et al[13]).

Figure 1 shows typical data from a study for measurement of the red value for the vocal folds over a course of treatment with a proton pump inhibitor for an individual patient.[12] Figure 2 shows data for the red value for a group of patients with chronic laryngitis symptoms during the course of treatment. Repeat examinations were scored for the red value for each visit. These data demonstrated that there was a measurable significant decrease in the color of red measured from the images of the vocal folds of patients as they were treated with acid suppression for chronic laryngitis symptoms.[12] Acoustic analyses of voice recordings of patients who presented with a complaint of hoarseness and other chronic laryngitis symptoms have demonstrated a significant change in measures of voice quality with acid suppression. There was a significant decrease in percent jitter (a measure of variability in voice frequency), as well as percent shimmer (cycle-to-cycle variability in signal amplitude), and there was a significant improvement in voice signal-to-noise ratio.[13] Figure 3 shows data on changes in acoustic measurements occurring during treatment of patients with chronic laryngitis who complained of hoarseness in that study.[13]

These data from patients with chronic laryngitis symptoms demonstrated that medication with the goal of blocking gastric acid secretion resulted in an objectively measurable decrease in one of the visible signs of inflammation in the larynx and also in quantified significant improvement in parameters of voice quality.

In a prospective treatment outcome study reported by Hanson et al,[4] more than 90% of the patients with idiopathic chronic laryngitis responded to antireflux treatment. In a progressively intense treatment regimen, patients were treated with lifestyle precautions against nocturnal reflux, subsequent addition of H2 blocker acid suppression for treatment failures, and substitution of a proton pump inhibitor at a progressively higher dosage for patients with continued symptoms. Recurrence of symptoms was common when treatment was discontinued, and patients who required proton pump inhibitors were more likely to have recurrence of symptoms when the acid inhibition was discontinued. Patients with more severe evidence of inflammation were more likely to require proton pump inhibitors to achieve resolution of symptoms and signs of laryngitis. About 50% of patients experienced resolution of laryngitis symptoms simply by following precautions to minimize the likelihood of experiencing reflux during sleep, and these subjects tended to have mild signs of laryngitis. About 25% of patients, who tended to have evidence of more severe inflammatory changes of the laryngeal tissues, were relatively resistant to treatment and required proton pump inhibitor acid suppression to achieve resolution of symptoms and signs of laryngitis.

Nevertheless, although there has been growing evidence in support of the hypothesis that reflux of gastric acid causes chronic laryngitis, it has not been proven that reflux of gastric contents including acid is the causative factor for the changes that have been documented in patients with chronic laryngitis symptoms. The clinical studies to date suggest that chronic laryngitis occurs in patients who may have minimal or no awareness of any reflux during waking hours. Many or most patients with chronic laryngitis do not show reflux on barium swallow studies, and most do not have endoscopic evidence of esophagitis.[3] Therefore, it seems that chronic laryngitis that is thought to be related to gastropharyngeal reflux is a disease process that is clinically different from gastroesophageal reflux disease. It would be highly desirable to be able to demonstrate a clear association between objectively documented episodes of reflux and the presence of laryngeal inflammation. The major problem in clearly establishing a causative relationship is documenting reliably when gastric reflux has occurred. There does appear to be an association of demonstrated acidification of the proximal esophagus and chronic laryngitis symptoms.[5]

Monitoring of esophageal pH demonstrates that gastric acid does reflux into the esophagus in individuals who do not have any esophageal or laryngeal complaints. Therefore, just detecting reflux into the esophagus is not helpful in selecting patients who will respond to treatment. A number of studies have associated the presence of esophagitis with the period of time that the esophageal pH is less than 4. However, there is considerable overlap in data between groups of normal subjects and groups of patients with symptoms of gastroesophageal reflux disease and no esophagitis. Further, as many as 23% of patients with esophagitis demonstrated by biopsy during endoscopy can be expected to show pH monitoring data that are within the range expected for normal control subjects.[14,15] Therefore, in the case of esophagitis (for which the best evidence exists for gastric acid reflux as the causative agent), in about one quarter of instances, pH monitoring will not document abnormal patterns in adult patients. With regard to supraesophageal disease, the American Gastroenterological Association has taken the formal position that "there are presently no prospective data showing that ambulatory esophageal pH monitoring can identify either patients with laryngitis or asthmatics that are likely to respond to anti-reflux therapy."[16]

CASE REPORTS EXEMPLIFYING PH DATA PROBLEMS

The following cases are illustrative of the unresolved problems in interpreting pH monitoring data for patients with chronic laryngitis.

Case 1. A 52-year-old man presented with complaints of recurrent throat irritation, a constant sensation of secretions in the back of the throat, and a chronic need to clear the throat. The voice quality was noted to deteriorate with voice use. Examination of the upper respiratory tract showed severe laryngeal inflammation, with erythema and hypervascularity of the posterior laryngeal mucosa. The patient had been under the care of a gastroenterologist for heartburn and hyperacidity symptoms in the past. After history and examination ruled out other apparent causes of chronic laryngitis, it was recommended that the patient follow nocturnal precautions against gastropharyngeal reflux and that he start a 2-month trial of proton pump inhibitor suppression of gastric acid. On subsequent multiple follow-up examinations, the patient noted improvement in the sensation of irritation and improvement in voice fluctuation, but never had resolution of his chronic throat-clearing, even with a relatively high dosage of 80 mg/d of the proton pump inhibitor. It was agreed that habitual throat-clearing was a factor in addition to whatever laryngeal inflammation may have existed at one time. The patient sought multiple opinions in several cities and underwent a pH monitoring study and endoscopy. The results of a double-probe pH study were reported as entirely normal, as were those of endoscopy. The patient was told that there was no evidence that he had any reflux problem, and he was advised to stop all acid suppression. Three months later, he returned with complaints of severe exacerbation of throat irritation, difficulty swallowing, and continued throat-clearing that was worse than before. Examination of the larynx showed marked dark erythema and edema of the posterior larynx, cobblestone granular changes of the posterior and supraglottic mucosa of the larynx, and marked hypervascularity and inflammatory edema of the vocal fold epithelium. The patient was advised to undergo repeat endoscopy, which showed erosive esophagitis. He was started back on proton pump inhibitor suppression. The strongly stated opinion, based on a "normal" pH study pattern, that this patient had no evidence of any reflux resulted in a severe exacerbation of reflux disease in both the esophagus and larynx that required a prolonged period of recovery.

Case 2. A 32-year-old woman presented with complaints of chronic sore throat, dysphagia, loss of voice with speaking, exercise-induced asthma, frequent laryngospasms and coughing, and neck nodularity for more than 5 years. On examination, she had severe laryngopharyngitis with dark erythema, edema and mucosal granularity, vocal process ulceration, and bilateral tender cervical adenopathy. She had been evaluated in several major medical centers in cities on both coasts. Results of 2 pH monitoring studies had been reported as normal. A 2-week trial of treatment with a proton pump inhibitor had not made significant changes in her symptoms. Thereafter, she had never been aggressively treated for reflux, and she had essentially become an invalid because of her symptoms. Because her symptoms and findings were highly suggestive of reflux-related laryngitis, the patient was convinced to undertake a treatment trial of nocturnal antireflux precautions and high-dose proton pump inhibitor therapy. At 3 months, she reported that the symptoms were essentially entirely resolved, and examination of her larynx and neck showed substantial improvement toward normal. She has remained free of symptoms with proton pump inhibition and lifestyle precautions. Because the results of her pH monitoring studies were considered to be normal, this patient had not had aggressive treatment for reflux and had suffered for several years.

Case 3. A 63-year-old man had been treated with full-course radiotherapy for a T1 carcinoma of the larynx. Two years after treatment, he presented for an opinion about his chronic severe hoarseness and cough. Examination showed erythema and hypervascularity of the entire laryngeal mucosa, with chronic laryngitis changes on both vocal folds. Laryngeal movements were normal. It was recommended that the patient follow precautions against reflux during sleep and that acid suppression with a proton pump inhibitor be initiated. The patient noted no improvement with halfhearted attempts at antireflux precautions and 20 mg of proton pump inhibitor per day. On follow-up examination, he had severe laryngeal inflammation, and there was new formation of posterior glottic granulation tissue and progressive limitation of arytenoid abduction. A double-probe 24-hour pH study was performed with the patient off medication, and the results were reported as normal. However, the severe inflammation of the patient's larynx continued to progress, with apparent posterior glottic stenosis. Although the pH study data had been interpreted as normal according to laboratory standards for range of duration of esophageal acidification, careful review demonstrated that there were actually several episodes of upper probe acidification during the night. The patient underwent direct laryngoscopy with cultures (negative) and biopsy (chronic inflammation). With some difficulty, the patient was convinced to follow antireflux precautions conscientiously and to begin a trial of high-dose (40 mg twice per day) acid suppression with a proton pump inhibitor. On follow-up examination, the laryngeal inflammation was noted to be markedly improved, as was the voice quality. There was no progression of the posterior glottic stenosis. On continued treatment, the appearance of the patient's larynx has continued to improve, as has his voice quality. In our clinical experience, chronic laryngitis is very often seen in patients who have been successfully treated for carcinoma of the larynx; it appears that the irradiated larynx tolerates reflux poorly. These patients may have evidence of severe inflammation but not complain of soreness or pain. Although this patient's pH data fell within normal limits, it appeared that the few episodes of upper esophageal acidification noted were indicative of sufficient reflux to cause severe damage to his irradiated larynx.

These are 3 examples of cases in which pH monitoring studies were unhelpful in identifying patients with chronic laryngitis symptoms that ultimately responded to antireflux and acid suppression treatment. It is quite common in our practice that patients respond well to antireflux treatment with complete resolution of symptoms even though they had undergone pH monitoring studies that had been reported as showing normal findings. On the other hand, there have also been instances in which pH monitoring has been helpful in patient management.

Case 4. A 45-year-old man complained of chronic sore throat, hoarseness, and dysphagia for dry foods. He had severe active reflux symptoms during the day, as well as symptomatic reflux that would awaken him from sleep. Treatment with H_2 receptor antagonists and antireflux precautions was not successful in alleviating either the symptoms or the appearance of severe laryngitis. A change of medication to a proton pump inhibitor at a dose of 40 mg/d also was not successful in alleviating the visible inflammation of the larynx or the patient's symptoms. A 24-hour pH monitoring study performed while the patient was taking 40 mg/d of the proton pump inhibitor demonstrated that the upper esophagus became "acidified" several times during the night. The dosage then was increased incrementally until, at 120 mg/d, the patient experienced complete relief of laryngitis symptoms and resolution of visible signs of laryngeal inflammation. The patient was advised to have a fundoplication, but to date, he manages his laryngitis successfully with medical acid suppression under the care of a gastroenterologist.

Our clinical experience reinforces the concern that there are a number of unanswered questions about the appropriate role of pH testing in the diagnosis and treatment of supraesophageal complications of gastric reflux. Several studies have reported pH data for patients with chronic laryngitis and compared them to data of control subjects, as well as to those of patients with reflux esophagitis. However, there is considerable variability in the reported data of pH monitoring in patients with chronic laryngitis symptoms. The rate of identified abnormal proximal-probe pH data in groups of patients with chronic laryngitis symptoms and signs has varied from less than 20% to as high as 80%.[2,5,17-19] Differences among studies can be attributed to differences in inclusion criteria and to differences in the technical aspects of data collection, as well as differences in interpretation of what constitutes an "abnormal" study result. However, as with data for biopsy-demonstrated esophagitis,[14,15] it seems reasonable to conclude that pH study data may not identify about 25% of patients who could ultimately respond to treatment. Therefore, it appears that pH monitoring is not the "gold standard" for identifying reflux causation of laryngitis, any more than it is for esophagitis.

The panelists who discussed these issues at the 1999 meeting of the American Broncho-Esophagological Association appear to agree that although pH monitoring can be helpful when a study result is clearly positive, a negative pH study result does not mean that the patient will not respond to antireflux treatment. In addition, there is agreement that a single distal probe is not adequate for evaluation of a supraesophageal disorder.[4] Positioning of the distal probe and proximal probe is critical. A study of control subjects with 5 concurrent readings spaced every 3 cm above the lower esophageal sphincter demonstrated a linear decrease in the percentage of time that the pH was less than 4 from the 3-cm level to the 15-cm level. The number of reflux episodes likewise decreases with more proximal positioning.[20]

It may be reasonable to position the proximal probe with endoscopic visualization without the use of manometry.[21] This technique may help standardize the recording site and the data derived from this proximal location. Also, endoscopic examination may show abnormalities of motility that are related to dysphagia symptoms. Hypopharyngeal sites for probe placement are currently used in some pH monitoring laboratories, but are considered inaccurate in others, because of the variability in the resistance of the transducer. The large volume of the hypopharynx may also increase the potential that a small volume of reflux might be missed, leading to a false-negative reading.[22]

It appears that the current consensus of the experienced clinicians on the panel is that the diagnosis of chronic laryngitis is based on identification of a history of characteristic symptoms and laryngoscopic findings. This is similar to the situation with esophagitis, for which the diagnosis is made endoscopically. The diagnosis of laryngeal or pharyngeal reflux differs, in that a biopsy is usually not done and may be contraindicated because of the possibility of a severe granulomatous response. If treated in a stepwise fashion, approximately 50% of patients will improve with lifestyle and behavioral changes alone. Therefore, it does not appear to be cost-effective or reasonable to subject this group of patients to 24-hour pH monitoring. An additional group of close to 25% of patients has a good response with the addition of an H2 blocker. Finally, most of the remaining patients (83%) will respond to therapy with a proton pump inhibitor.[4] Therefore, there appears to be consensus on the following indications.

INDICATIONS FOR 24-HOUR pH PROBE STUDY IN MANAGEMENT OF CHRONIC LARYNGITIS

A double-probe pH study is probably indicated if evidence of chronic ongoing moderate-to-severe laryngitis persists when the patient has been compliant with antireflux precautions and has been on an adequate dosage of a proton pump inhibitor for at least 6 to 12 weeks. The pH study is usually performed with the patient on medication to document the adequacy of therapy.[23]

In general, a pH monitoring study is usually recommended as a baseline study before Nissen or Toupet fundoplication. This is especially true if the surgery is proposed for treatment of chronic laryngitis without findings of esophagitis on endoscopy. In this instance, the double-probe pH study is performed after withholding antisecretory therapy for 1 week or more.[23] The third indication for a pH monitoring study is to evaluate the efficacy of a fundoplication procedure in patients who have continued or recurrent symptoms after fundoplication.[24]

CONCLUSION

The clinical diagnosis of chronic laryngitis is based on the patient's symptoms and on endoscopic laryngeal findings. This diagnosis differs from that of esophageal disease, in that a biopsy of the larynx is not routinely performed. No prospective study has demonstrated that pH probe evaluation has specific predictive value for identifying patients with chronic laryngitis who will respond to therapy. Further, patients with symptoms and findings of chronic laryngitis are likely to generate an abnormal pH probe recording only approximately 50% of the time. Nevertheless, 24-hour double-probe pH recording may be useful in patients in whom therapy (reasonable or comprehensive) has failed. Identification of hypersecretors may help direct further treatment. Finally, double-probe recording may provide useful additional information before recommendation of a fundoplication or in evaluation of a failed fundoplication. Further work is indicated to identify better ways of demonstrating the causative relationship of laryngopharyngeal reflux to chronic laryngitis. Although the acidic characteristic of refluxed material appears to clearly be important, the pH may not be the only important factor in causation of the injury to the tissues that is seen with chronic laryngitis thought to be due to laryngopharyngeal reflux.

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AMBULATORY PH MONITORING METHODOLOGY

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Twenty-four–hour ambulatory double-probe pH monitoring is the current "gold standard" for the evaluation of gastroesophageal and extraesophageal reflux. The following article seeks to characterize some of the areas of controversy and describes the methodology of ambulatory pH monitoring used at the Center for Voice Disorders of Wake Forest University.

KEY WORDS — gastroesophageal reflux, laryngopharyngeal reflux, pH monitoring, pH probe, pH testing, reflux.

INTRODUCTION

In general, ambulatory 24-hour pH monitoring is considered the current "gold standard" for reflux testing. However, in otolaryngology practice, there is no consensus concerning the number of sensors, their precise location, or the interpretation of the results. Is a pharyngeal sensor always necessary? How should a reflux event be defined? To what degree (if any) is extraesophageal reflux normal?

NEED FOR PHARYNGEAL SENSOR

Double-probe (simultaneous pharyngeal and esophageal) pH monitoring is superior to diagnostic methods such as barium swallow study, endoscopy, and single-probe esophageal pH testing, because it is both sensitive and specific.[1-4] In fact, double-probe testing (2 sensors) is required to properly interpret the findings of the proximal sensor, whether it is in the pharynx or the proximal esophagus. When the pharyngeal probe is positive, according to appropriate criteria, it is diagnostic of extraesophageal reflux (EER). The importance of the pharyngeal sensor cannot be overestimated. Katz[5] initially showed in a small number of patients that relying solely on an esophageal probe would yield a number of falsely negative results regarding EER. A recent review of pH measurement data at the Center for Voice Disorders of Wake Forest University demonstrated that 59% (155 of 262) of a consecutive series of patients with documented EER had normal upright, supine, and total esophageal acid exposure times in their esophagus (Center for Voice Disorders, unpublished observations, 1999). Therefore, in a highly select group of patients with otolaryngological complaints, 59% of the patients would have been inappropriately assumed to not have EER if the pharyngeal sensor had not been used. Similarly, in the pediatric population, Little et al[6] have shown that the pharyngeal probe is equally important. They demonstrated that 46% (78 of 168) of children with documented EER had normal esophageal acid exposure times.

It is clear that measuring distal esophageal acid exposure does not allow us to make assumptions concerning EER. Therefore, is a proximal esophageal sensor of any practical benefit, and if so, where do we place the more proximal probe?

PROXIMAL ESOPHAGEAL REFLUX

Weusten et al[7] looked at the dynamic characteristics of reflux using a probe with 5 ion-sensitive field effect transistor pH transducers. They showed a nearly linear decrease both in acid exposure times and in the number of reflux episodes as one moves more proximally in the esophagus. In fact, in asymptomatic adults, the mean esophageal acid exposure time 6 cm from the lower esophageal sphincter (LES) was only 77% of that found at 3 cm. This difference demonstrates the importance of using manometry to place the distal probe precisely at 5 cm from the LES. This position (5 cm from the LES) is based on convention and is the "benchmark" for research and clinical use. Years of study have produced well-established normative data for esophageal acid exposure 5 cm above the LES, and using this as a reference point in the study of gastroesophageal reflux (GER) and EER remains important. In addition, data from this location are particularly crucial when considering the possibility of a fundoplication. Small changes in the position of the esophageal sensors will have a significant effect on the results in both adults and children.[8-10]

It has been demonstrated by various groups that proximal esophageal reflux in normal patients is a very uncommon event, and its direct relationship to EER remains to be determined.[11-13] Some institutions

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are using manometrically placed 3-site pH monitoring.[14,15] The distal probe is 5 cm above the LES, and the pharyngeal probe is approximately 2 cm above the upper esophageal sphincter (UES). The proximal esophageal sensor would then be 10 cm distal to the pharyngeal probe, and hence usually about 4 to 6 cm below the UES. The data obtained from these studies are interesting in the evaluation of the characteristics of GER and EER, but the proximal esophageal probe itself does not add relevant clinical information at this time nor answer the key question, that is, the presence or absence of EER.

Measuring gastric pH and using it to extrapolate results regarding GER is clearly invalid. In a similiar manner, using esophageal pH testing at any proximal location to confirm or "prove" the presence or absence of EER is highly questionable at best, because the UES functions as the final barrier limiting EER. In addition, acid instillation into the esophagus increases the UES resting pressure, thereby enhancing its effectiveness as a barrier to EER.[16] Further large studies that use 2 or 3 esophageal sensors with a pharyngeal sensor will be needed to further evaluate this issue.

AMBULATORY pH MONITORING TECHNIQUE

Equipment. The standard components used for ambulatory pH monitoring are a pH probe, a manometer for placement, a data storage device, and appropriate computer software. The most common types of pH probes in use today have antimony sensors with varying intersensor distances. In comparison to other types of probes, they are reasonably inexpensive and are quite durable. They are less sensitive than probes with glass sensors, but the clinical difference is not significant. They are semidisposable, lasting for three to eight 24-hour testing periods. These probes are flexible and do not present difficulty in transnasal passage or swallowing.

A manometer is necessary for probe placement. Solid-state manometers are simple to use and provide easily interpretable studies. Although more expensive than water-perfused manometers, they have no openings and are therefore very easy to clean and maintain, although they are more easily broken. Data storage devices are worn over the shoulder or around the waist during the period of testing. These gather data from 1 or 2 sensors. One key feature is an event marker. This enables the patient to mark the data at the point at which various events or symptoms occur. The actual nature of the symptom itself is described in the patient's diary and later correlated with the pH results.

Commercial pH measurement software is readily available. This allows numerical and time course surveys from the probe to be categorized. Some software packages generate severity scores such as the DeMeester score, statistical analysis, and various types of pH curves, and others allow customization for clinical and/or research purposes and for producing specialized reports. We currently use a 4-channel "Castell"-type solid-state manometry catheter with esophageal motility analysis software for the LES, UES, and esophageal body; antimony monocrystant semidisposable dual-sensor pH catheters; a Mark III microdigitrapper (4Mb) (all from Medtronic Functional Diagnostics, Shoreview, Minn); and a computer with a laser printer.

Current Techniques. At our center, all patients stop taking proton pump inhibitor medications at least 1 week before the study. H2 blockers and gastric motility drugs are stopped 4 days before the study. No antacids are taken within 6 hours of the test or during the study itself. Esophageal manometry is initially performed after the most patent nostril has been decongested and a small amount of lidocaine has been applied. The solid-state manometer is inserted transnasally, and the patient is allowed a 5-minute period to acclimatize himself or herself to it. The station pull-through technique is used to determine the location and length of both sphincters. Esophageal body motility is also assessed on a series of wet and dry swallows. The distance from the nose to the upper edge of both the LES and the UES is noted.

Probes are available with various intersensor distances (10, 15, 18, 20, 21, 22, 24, and 26 cm apart), allowing a probe to be selected that will place the distal esophageal sensor 5 cm above the LES and the proximal sensor at the superior border of or just above the UES. Practically, this is done by measuring the distance from the nose to the superior extent of both the LES and UES (for example, 40 and 17 cm, respectively). Placing the distal sensor 5 cm above the LES results in that sensor's being 35 cm from the nose. Seventeen centimeters (nose to UES) subtracted from 35 cm (nose to distal sensor) gives an intersensor distance of 18 cm. Therefore, using a pH probe catheter with an 18-cm intersensor distance will place the proximal sensor just above the UES.

The pH sensors are calibrated in pH 7 and pH 1 buffer solutions before the initiation of each study. The presence or absence of gastric acid is documented by advancing the distal probe into the stomach and then withdrawing it to the position previously determined by manometry. The sensors are then connected to the digitrapper. All patients are reminded to perform their normal daily activities and to not restrict their diet with the exception of the use of antacids. Specifics regarding their diary are reviewed. Significant time must be spent explaining how valuable an accurate diary is during the test. It is important to note not only times of eating or drinking, but also when the individual is lying down or sleeping and when any symptoms are occurring. The following morning, the probe is removed and the data are downloaded into a computer for analysis and printing.

The data obtained include the percentage of time the pH was less than 4 in the upright and supine positions, as well as the total time. Episodes greater than 5 minutes, the longest upright episode, the longest supine episode, and the total number of episodes are recorded. The diary is reviewed with the patient, and symptom correlation is determined. Pharyngeal episodes are documented as occurring in the upright or supine position with a pH of less than 4 or a pH of less than 5. Specific criteria are used to determine whether an EER event has or has not occurred.

Another technique for ambulatory pH measurement relies on fiberoptic laryngoscopy to guide the insertion of the pH probe.[17] A double-probe pH catheter is inserted under direct vision so that the proximal sensor is just surrounded by the mucosa of the esophagus. The distal probe is located 15 cm from this point (a fixed distance). Comparison of this technique with manometry shows that direct visualization results in the proximal sensor's being placed in an adequate position. This technique is adequate for the detection of EER; however, not knowing the precise location of the distal probe in relation to the LES prevents a definitive determination of the presence or absence of GER. If fundoplication surgery is under any consideration at all, then the data from a precisely placed distal sensor are vital. Comparing this technique with manometric-guided methods in a large group of patients may prove interesting.

Some centers advocate using a fixed-length probe with the proximal sensor located 2 to 6 cm below the UES and the distal sensor 5 cm above the LES. This method has the same limitations noted earlier.[11,18]

Diet. At our center, we allow patients to eat a normal, "ad libitum" diet, which makes the testing representative of each individual's unique situation and lifestyle. Although some institutions advocate a controlled diet or some types of dietary restrictions during pH monitoring, we do not believe this is beneficial. Reflux appears to have a great deal of day-to-day variability that is at least in part due to diet.[4] The period of time tested should reflect the individual's home and occupational environment. If an individual has an excessively large lunch or dinner as a matter of practice, then this should be allowed to take place. In addition, individuals are allowed to smoke and drink alcohol as they would normally.

DEFINITION OF REFLUX EVENT

Early ambulatory pH measurement studies using a pharyngeal probe were occasionally flawed by the occurrence of "pseudoreflux" events.[1,18-20] These were believed to be secondary to placement of the pharyngeal sensor high in the hypopharynx, allowing significant changes in the impedance of the circuit, depending on whether the sensor had dried or was in direct contact with the hypopharyngeal mucosa. This problem is now uncommon, because of improved sensors, probe placement just above the UES, and use of rigid interpretation criteria to define pharyngeal reflux episodes.

Criteria for defining reflux are 1) the pH decreases to less than 4; 2) the pharyngeal pH drops during or immediately after distal esophageal acid exposure; 3) the pH drop does not occur during an episode of eating or swallowing; and 4) the proximal sensor pH drop is rapid and sharp, not gradual. Some authors also believe that the hypopharyngeal pH drop should be greater than 3 pH units, but this criterion is not used at our institution.[20] Applying these criteria and ensuring proper probe placement will minimize episodes of pseudoreflux.

Recent work regarding the function and stability of human pepsin shows it to be active at a pH of 5. Therefore, using this level as a defining point for EER may be more valid.[11,21] Using a pH of 5 as indicative of reflux in the proximal esophagus may also be valid, because proximal acid exposure times are quite low, and the dilutional and neutralizing factors present in saliva are greater at this level.[11]

NORMAL VALUES

Esophagus. Normal values for proximal *intra-esophageal* acid contact vary somewhat between institutions, but are rather consistent.[11,22,23] It has been shown that more proximally up the esophagus, there is a progressive decrease in esophageal exposure time and the number of reflux events. Immediately distal to the UES, the total esophageal acid exposure time should be less than 1%; upright time with the pH at less than 4 should be less than approximately 1.5%; and no episodes should be detected when the patient is supine.

Pharynx. The establishment of normal values for the pharyngeal sensor is far more controversial: is EER normal? The nature of the larynx, pharynx, and upper airway makes them quite susceptible to acid-induced injury. In contrast to the esophagus, the laryngopharynx does not have effective defense mechanisms to combat acid- and peptic-induced injury once the UES is breached.[22] It is clear that in the setting of laryngeal or subglottic injury, a single EER event has great clinical significance. However, is occasional EER in an asymptomatic individual abnormal? Because of work by Little et al[24] in the injured canine subglottis and the work of Delahunty and Cherry,[25] it has been assumed that any extraesophageal acid contact is pathological in nature. Koufman,[1] testing 20 asymptomatic controls, demonstrated no evidence of EER. However, it does appear that the overall condition of the larynx and pharynx is a major contributing factor, and studies have shown limited extraesophageal acid contact in entirely asymptomatic individuals.[14,15] In fact, one study documented pharyngeal acid reflux events in as many as 20% of normal controls.[14] Smit et al[17] have stated that perhaps as many as 3 EER events over 24 hours may be normal. However, their brief report did not mention laryngeal examinations or whether there were complaints suggestive of EER.

Such individuals with asymptomatic EER may be at risk for laryngeal and subglottic damage in the event that their larynx or airway is traumatized. A "normal" individual with asymptomatic EER could have intubation or vocal abuse that could readily lead to the development of laryngeal or subglottic edema, granulation tissue, granuloma formation, or posterior glottic and/or subglottic stenosis. Inflammation or injury before reflux may be the single most important variable.[24] Such a mechanism is most probably at work in individuals who undergo brief periods of intubation and then present with subglottic stenosis.[1,14]

In this author's opinion, judging whether a given patient's EER found during prolonged pH monitoring is abnormal can only be done on an individual basis. In a patient with subglottic stenosis, laryngeal edema, leukoplakia, or recurrent granuloma, a single episode of EER would be considered highly significant and complete acid suppression would be warranted. One or 2 pharyngeal reflux events in an entirely asymptomatic person with normal findings on laryngeal examination may be of little importance *unless* he or she is intubated, undergoes laryngeal surgery, or abuses his or her voice.

pH MEASUREMENT VARIABILITY

Extraesophageal reflux is often intermittent in nature, and therefore the diagnosis is not always straightforward, because a negative pH study does not rule out EER.[1,19] The difficulty in confirming the diagnosis of EER is well demonstrated in a study by Vaezi et al.[13] Thirty-two individuals were studied on 2 occasions by means of ambulatory double-probe pH monitoring with the distal sensor 5 cm above the LES and the proximal sensor just below the UES. The tests were performed within 20 days of one another. The placement of the probe just below the UES was done to limit the possibility of detecting pseudoreflux events. This study showed that there was significant day-to-day variability of pH in the proximal esophagus. Healthy volunteers had good intrasubject reproducibility (91% to 100%). Those with distal reflux and proximal reflux had poorer reproducibility (distal, 70% to 90%; proximal, 55%). This outcome demonstrates good specificity but poor sensitivity for the detection of proximal reflux during any single 24-hour test period. Also, the variability would increase if test periods of less than 20 to 24 hours were used.

SUPRAESOPHAGEAL COMPLICATIONS DUE TO GER

Although the major consideration of this report is methods of ambulatory pH monitoring in patients with suspected complications of reflux disease, the importance of vagal reflexes cannot be forgotten. In individuals with asthma or recurrent exacerbations of chronic obstructive pulmonary disease, it has been demonstrated that vagally mediated reflexes from the esophagus (GER) have a highly deleterious effect on pulmonary function. This reflex-mediated response can occur *without* EER. In fact, the primary etiology of the pulmonary manifestations of reflux disease may be secondary to vagally mediated reflexes, laryngeal contact with acid or microaspiration, or some combination of the above.[23,26-28] In addition, there is some suggestion that sinus disease and possibly even some otologic problems may in some way be associated with reflux.[29] Whether this association is due to direct contact with the refluxate or, more probably, some type of undetermined neurogenic reflex remains to be determined.

SUMMARY

Although more work characterizing and standardizing prolonged pH monitoring in otolaryngological patients remains to be done, certain points are important: 1) double-probe studies are necessary; 2) the pharyngeal sensor is critical; and 3) further research in this evolving area is warranted, with particular attention to controls and defining normals.

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APPLICATION OF AMBULATORY 24-HOUR MULTIPROBE PH MONITORING IN THE PRESENCE OF EXTRAESOPHAGEAL MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX

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The recognition of extraesophageal manifestations of gastroesophageal reflux (GER) has gained acceptance in recent years. Objective measurements of acid reflux have been aided greatly by the advent of multiprobe pH monitoring. The development of the multiprobe pH monitor has enabled researchers and clinicians to objectively measure acid exposure in the pharynx and upper esophagus. The indications for use of this diagnostic technique for a variety of extraesophageal manifestations of GER are outlined.

KEY WORDS — extraesophageal reflux disease, gastroesophageal reflux disease, pH monitor.

Gastroesophageal reflux disease (GERD) is estimated to affect as many as 75 million Americans.[1] It has been estimated that as many as 50% of patients with GERD experience some type of atypical (extraesophageal) manifestation of gastroesophageal reflux (GER), often without esophageal symptoms.[2] These include pulmonary, laryngeal, tracheal, nasosinal, orodental, otologic, and other symptoms. Although a strong clinical association between acid reflux and many of these extraesophageal manifestations has been known for more than 30 years, objective correlation has for the most part been lacking. With the introduction of prolonged pH monitoring by Miller et al[3] in 1964, the initial report of clinical standards by Johnson and DeMeester[4] in 1974, and the advent of multiprobe pH monitoring in the late 1980s, a method for quantitatively identifying reflux events was established as the gold standard for identifying GERD. Nevertheless, many issues exist regarding pH probe monitoring and its application to extraesophageal manifestations of GER.

In 1968, Delahunty and Cherry[5] initially described the relationship between acid reflux and posterior laryngeal granulomas. Since that time, a number of clinical studies have further described the effects of GER in the larynx. The typical signs include interarytenoid erythema, edema, nodularity, ulceration, and granuloma, whereas the classic symptoms are frequent throat-clearing, cough, and globus pharyngeus.[6] The association with acid reflux had traditionally relied on barium swallow study with cinefluoroscopy; however, the sensitivity and specificity for this test were poor. Single-probe 24-hour pH studies evaluating the presence of reflux in patients with laryngeal manifestations were equivocal at best. Wilson et al[7] demonstrated positive acid reflux in only 17.5% of patients with posterior laryngitis. Koufman,[8] on the other hand, using double-probe 24-hour pH monitoring, found abnormal results in nearly 70% of patients with typical posterior laryngitis and in more than 90% of patients with subglottic stenosis.

The single greatest advantage of multiprobe 24-hour ambulatory pH monitoring is the ability to demonstrate reflux over the course of an entire day. By following the daily cycle of the patient, the technique has a better chance of capturing intermittent reflux events. In addition, recent technical advances in the composition and gauge of the probe have increased patient tolerance.

Otolaryngologist acceptance has increased with the recently described technique of probe placement with a flexible telescope, which eliminates the need for manometry. However, several considerations must be taken into account. The definition of a positive pH study result varies from laboratory to laboratory. The presence of a pH level of less than 4 more than approximately 5% of the time is generally considered a positive result for the esophageal probe. For the pharyngeal probe, however, many believe that a single event may be significant. If this is indeed the case, then the question arises whether 24 hours is long enough, especially if dietary restrictions are maintained during the study (eg, avoidance of acidic beverages). Another consideration is the potential for a vagally mediated response even in the absence of significant reflux. Several studies have demonstrated that vocal fold granulomas occur despite aggressive reflux therapy or in the absence of "significant" acid

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reflux, and that some of these recalcitrant granulomas responded to neuromuscular blockade of the thyroarytenoid muscle.[9] This finding may imply an abnormal vagal response to physiological reflux at the distal esophagus. A similar theory has been advocated for asthma,[10] sudden infant death syndrome,[11] and cricopharyngeal spasm.[12]

Clearly, multiprobe pH monitoring offers the otolaryngologist the ability to detect abnormal esophageal and/or pharyngeal acid reflux; the question remains, where does this method fit in the management of the patient? Because the test is not 100% sensitive, especially given the intermittent nature of atypical GER, it would seem prudent to attempt an empiric trial of therapy in patients who have typical laryngeal manifestations of GER. Controversy exists as to what constitutes an adequate trial of therapy; however, in my practice this generally consists of a 12-week course of a twice-daily proton pump inhibitor, a prokinetic agent, antacids at meals and bedtime, dietary advice, and elevation of the head of the bed. If this therapy does not result in resolution of symptoms, then I perform a double-probe 24-hour ambulatory pH test with the patient on medication. If reflux is documented, then proton pump inhibitor doses are doubled. If symptoms still persist or if doses cannot be reduced after 6 months, an endoscopic surgical reflux correction is indicated. Even with severe laryngeal manifestations of GER, actual reflux events, particularly pharyngeal events, are often intermittent. Therefore, if high clinical suspicion exists, a repeat pH study is indicated. Of note, clinical signs of improvement often lag behind symptomatic improvement; therapy discontinuation generally is based on symptomatic improvement.[13]

As mentioned earlier, studies have demonstrated a probable correlation between adult subglottic stenosis and GER. Gaynor[14] demonstrated in a rabbit model that severe subglottic mucosal changes occur when pepsin is combined with decreasing pH. He also studied 20 intubated patients in the intensive care unit and found that 40% had pH levels of less than 4. Jindal et al[15] reported on 7 women with idiopathic subglottic stenosis who required reflux therapy for resolution. Because reflux therapy appears to be required once the diagnosis of subglottic stenosis is made, it is prudent to initiate aggressive reflux therapy as described above. Certainly, if surgery is anticipated, therapy should begin before surgery. In my practice, I perform a 24-hour ambulatory pH monitoring study after 2 weeks of therapy, because of the potentially devastating effects of continued acid reflux in patients with subglottic stenosis. Similarly, after a 6-month course of aggressive therapy, if the patient continues to have reflux when taken off medications, endoscopic fundoplication is recommended.

Pulmonary symptoms attributed to GER include chronic cough, bronchitis, and asthma. Three mechanisms are proposed. The first is direct microaspiration of gastric materials into the pulmonary tree. The second involves a vagally mediated response in which distal esophageal distention initiates a bronchospastic response. The third is a combination of both. The diagnosis tends to, again, be one in which an empiric approach is used; however, there is a particular difficulty in treating asthmatic patients with GER. Beta agonist bronchodilators are known to relax the lower esophageal sphincter in a dose-related fashion. Thus, there may be an indication to evaluate patients with asthma by using beta agonists with multiprobe 24-hour pH measurement to possibly determine adjustment of therapy.[16]

Irwin[17] contends that a specific diagnosis is obtainable in 88% to 100% of patients with chronic cough. Smyrnios[18] found GER to be the cause of chronic cough in approximately 20% of referred patients with a cough of unknown origin. Furthermore, studies have indicated that as many as 75% of patients have cough as the only symptom of their reflux disease. An adequate workup includes a medical history (especially postnasal drip and allergy), medications (especially angiotensin-converting enzyme inhibitors), and therapeutic trials of antihistamines and steroids. In Smyrnios' study, the diagnostic tests, in order of usefulness, were sinus x-ray, spirometry with and without methacholine challenge, barium cine-esophagography, 24-hour pH study, chest x-ray, and bronchoscopy. Irwin et al[19] contend that once asthma and postnasal drip have been ruled out, GER is a likely source of symptoms. On this basis, they advocate a low-fat, high-protein diet that restricts foods that decrease lower esophageal sphincter pressure. In addition, aggressive medical therapy, including a twice-per-day proton pump inhibitor and prokinetic agents, is prescribed. If this regimen does not improve symptoms, then a pH study is recommended. If the study shows continuing reflux events on medication, then fundoplication is recommended.[19]

Chronic sinusitis is a common condition — the eighth most common diagnosis in the United States.[20] The etiology, diagnosis, and treatment of this condition are not within the scope of this short discussion; however, several recent papers have drawn attention to GER as a potential etiologic factor. Contencin and Narcy[21] used a single-probe pH monitor placed in the nasopharynx in 13 children with nasosinal disease and 18 control subjects. Reflux events were significantly greater in the rhinitis group. Chambers et al[22] looked at a number of potential factors that may contribute to the failure of sinus surgery. Only the presence of GER was found to have significance in predicting a poor outcome. El-Serag and Sonnenberg[23] surveyed more than 100,000 US Veterans Administration patients with the diagnosis of esophagitis and found sinusitis to be the most common comorbid condition. Certainly, in patients with refractory sinusitis, GER should be considered. It would seem that if sinus surgery fails in a patient, a 24-hour double-probe ambulatory pH study or a therapeutic trial of aggressive antireflux medication might be indicated; however, further study is needed.

The recognition of extraesophageal manifestations of GER has steadily gained acceptance in the medical community. Atypical GER represents a disease with a broad constellation of symptoms that crosses traditional specialty lines. Although challenging, this entity provides a great opportunity for collaboration and mutual understanding. In this milieu, it is not surprising that a diagnostic tool developed by gastroenterologists and thoracic surgeons — the multiprobe pH monitor — has found applications among pulmonologists, otolaryngologists, and others. Technical advances such as multilevel sensors, single and thinner catheters, user-friendly software, and decreasing cost have all contributed to the monitor's greater usage. Improvements in sensitivity and specificity and further refinements are on the horizon. These will no doubt increase the indications for use in the future.

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VALUE OF PH PROBE TESTING IN PEDIATRIC PATIENTS WITH EXTRAESOPHAGEAL MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX DISEASE: A RETROSPECTIVE REVIEW

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Extended pH probe testing is often performed in patients believed to have extraesophageal symptoms of gastroesophageal reflux disease (GERD), although for this indication its diagnostic value is not well established. A retrospective review of all patients who underwent pH probe testing between 1994 and 1998 was conducted to determine the outcome of antireflux therapy in the subgroup with probable extraesophageal symptoms of GERD. Sixty-eight patients underwent antireflux therapy and had adequate follow-up after pH probe testing to be included in the study. Fifty-eight patients (85%) responded to antireflux therapy (improved, 44%; cured, 41%). The positive predictive value of distal pH probe testing was greater than 90%, but the negative predictive value was less than 50%. The reproducibility of pH probe testing on different study days was poor, but pH probe testing was helpful in assessing the adequacy of antireflux therapy. The presence of gastrointestinal symptoms did not correlate with the response of extraesophageal symptoms to antireflux therapy. Thirteen patients underwent double-probe pH studies. The mean percent time the pH was less than 4 in the upper esophagus was 2.6% (range, 1% to 9.6%). Twelve of these patients were improved or cured with antireflux therapy. Distal pH probe testing is of limited benefit in predicting whether patients with extraesophageal symptoms of GERD will respond to antireflux therapy. If extraesophageal symptoms of GERD are suspected, patients should undergo an empiric trial of antireflux therapy. Distal pH probe testing should be reserved for assessing the adequacy of antireflux therapy if symptoms persist. A prospective, randomized, controlled study will aid in determining the predictive value of double-probe pH studies in pediatric patients with probable extraesophageal symptoms of GERD.

KEY WORDS — extraesophageal reflux disease, gastroesophageal reflux disease, larynx, pH, supraesophageal reflux disease.

INTRODUCTION

Gastroesophageal reflux (GER) is a common physiological event that affects infants and children. When reflux events cause symptoms or histologic changes, the process is pathological and is referred to as gastroesophageal reflux disease (GERD); GERD most commonly causes gastrointestinal manifestations, but may cause or exacerbate other conditions and cause "extraesophageal symptoms." These manifestations include apnea, chronic cough, recurrent pneumonia, hoarseness, aspiration, dysphagia, stridor, subglottic stenosis, pharyngeal complaints, and Sandifer's syndrome.[1-7] Establishing GER as a causative or exacerbating factor in patients with these problems is difficult, particularly if other signs or symptoms of reflux are absent. Although extended pH probe testing is considered the gold standard for diagnosing reflux events, the value of this study in extraesophageal GERD has not been well established. This retrospective study was undertaken to determine whether pH probe testing is predictive of a response to antireflux treatment in patients with probable extraesophageal symptoms of GERD.

MATERIAL AND METHODS

We performed a retrospective chart review of all patients who underwent single-probe or double-probe pH testing in the Division of Pediatric Gastroenterology at the University of Iowa during a 5-year period beginning in 1994. Placement of the distal pH sensor 3 to 5 cm above the lower esophageal sphincter was confirmed radiographically. In patients who underwent double-probe pH studies, the upper (proximal) sensor was placed in the middle to upper esophagus, 5 cm superior to the distal probe in infants and 10 to 15 cm superior to the distal probe in toddlers and older children. Age, presenting symptoms, and pH probe results were recorded, the last as the Euler-Byrne score and the percentage of time the pH was less than 4. The Euler-Byrne score is calculated as $x + 4y$, where x is the number of reflux events and y is the number of events lasting more than 5 minutes; scores greater than 50 are considered abnormal.[8] For the distal probe, more than 5% total time with a pH

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TABLE 1. STUDY DATA

	No. of Pts
pH probe studies completed	155
Gastrointestinal symptoms only	41 (26%)
Extraesophageal symptoms	114 (74%)
Antireflux trial and follow-up	68
Inadequate follow-up	10
No antireflux trial	35
Technical problem with pH study	1

less than 4 was considered abnormal[9]; values for proximal recordings have not been uniformly established.

Patients were included in the study if they underwent pharmacological or surgical antireflux therapy and had adequate medical follow-up by the Department of Otolaryngology–Head and Neck Surgery or the Division of Pediatric Gastroenterology. Age-based, conservative (nonpharmacological) antireflux therapy was recommended to all patients and their caretakers. For infants, this recommendation included small-volume, frequent feedings thickened with rice cereal. Prone positioning, although beneficial in reducing the number of reflux events,[10] was not recommended because of concerns of increased risk of sudden infant death syndrome.[11] Older children were instructed to avoid large meals and to refrain from eating for 2 to 3 hours before bedtime. Abstinence from chocolate, licorice, caffeinated products, carbonated beverages, and highly seasoned foods was advised.

Pharmacological antireflux therapy was not standardized. Early in the study, a promotility agent (Propulsid or metoclopramide) in combination with an H2 receptor antagonist (ranitidine or famotidine) was favored. Later, once- or twice-daily proton pump inhibitors (PPIs; omeprazole or lansoprazole) were used with or without a promotility agent. Parents were counseled that PPIs have not been approved by the US Food and Drug Administration for use in children.

The outcome of antireflux therapy was assessed 6 to 8 weeks after initiation of therapy. The response to therapy was recorded as "cured," improved," or "unchanged" as determined by the parent's or caretaker's response to questions posed by the evaluating physician. Children who were "nearly completely cured" were considered improved. The pH probe results in responders (cured or improved symptoms) were compared with those in nonresponders (unchanged symptoms) by the Wilcoxon 2-sample test, with p values less than .05 considered statistically significant. The positive predictive value of the pH probe study, based on the outcome to antireflux therapy, was calculated as the number of responders divided by the number of predicted responders. The negative predictive value was calculated as the number of nonresponders divided by the number of predicted nonresponders.

RESULTS

One hundred fifty-nine pediatric patients underwent pH probe testing during the study period. The medical records of 155 patients were available for review (Table 1). Gastrointestinal manifestations alone, in the absence of extraesophageal symptoms, were noted in 41 of 155 patients (26%). The remaining 114 patients (74%) had possible extraesophageal manifestations of GERD. Sixty-eight patients underwent a trial of antireflux therapy and had adequate follow-up (4 months to 4 years) to assess the efficacy of therapy. These 68 patients are the subject of this review.

Extraesophageal Symptoms. The frequency and types of extraesophageal manifestations in the children included in this report are outlined in Table 2.

TABLE 2. PATIENT DATA

			*Responders**		*Nonresponders**
Symptom	*No. of Patients*	*Mean Age (Range)*	*No. Cured/ No. GI Symptoms*	*No. Improved/ No. GI Symptoms*	*No. Unchanged/ No. GI Symptoms*
Chronic cough	28	3.1 y (1 mo to 11.5 y)	12/8	14/5	2/1
Apnea	21	1.0 y (1 mo to 6 y)	12/4	4/1	5/3
Recurrent pneumonia	9	2.7 y (3 mo to 6 y)	5/2	4/0	0/0
Aspiration	6	1.3 y (1 mo to 2.5 y)	5/5	0/0	1/0
Dysphagia	7	6.6 y (1.5 mo to 15 y)	3/0	4/2	0/0
Stridor	7	2.1 y (3 wk to 7 y)	1/0	5/2	1/1
Hoarseness	5	2.3 y (8 mo to 5.5 y)	3/2	1/0	1/0
Sinusitis	7	3.9 y (2 y to 9 y)	2/2	4/1	1/1
Pharyngeal†	8	6.2 y (3 y to 11 y)	1/0	6/4	1/1

GI — gastrointestinal.

*Twenty-eight patients had 2 extraesophageal symptoms, and 2 patients had 3 extraesophageal symptoms.

†Pharyngeal symptoms included sore throat, aphthous stomatitis, and chronic throat-clearing.

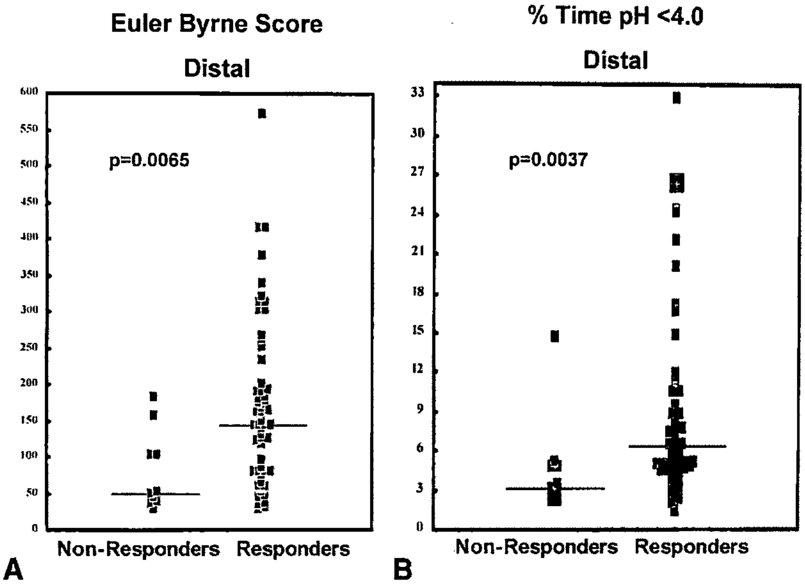


Fig 1. Distal pH probe data in pediatric patients in whom extraesophageal symptoms of gastroesophageal reflux disease were suspected. A) Median Euler-Byrne scores for patients who responded to antireflux therapy (Responders) and for patients who did not respond to antireflux therapy (Non-Responders). B) Median percent time pH was less than 4 for distal reflux events in same patient population.

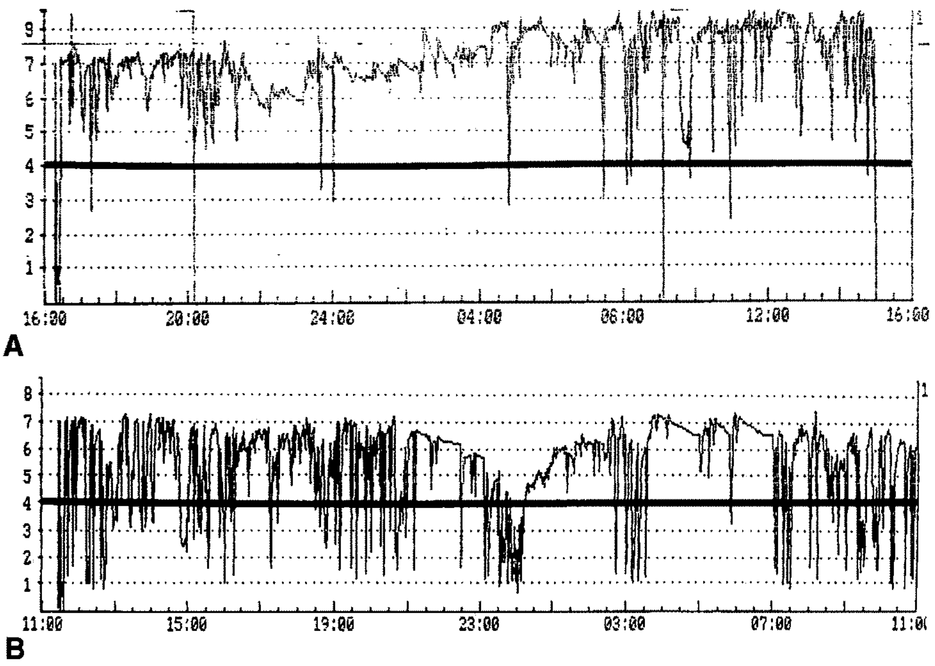
Twenty-seven patients had 2 extraesophageal symptoms, and 2 patients had 3 extraesophageal symptoms. Of note, concomitant gastrointestinal symptoms of emesis, pyrosis, stomach pain, water brash, and inadequate oral intake with failure to thrive were absent in 60% of these patients.

Response to Therapy. Caretakers reported that 41% of patients with extraesophageal manifestations who underwent antireflux therapy were cured of their symptoms, 44% were improved, and 15% remained unchanged. Of the 58 patients who responded to therapy, 14 had undergone fundoplication or revision fundoplication. Fundoplication was not performed in any subjects in the group of nonresponders. The response to therapy based on symptom presentation is illustrated in Table 2.

Diagnostic Value of Distal pH Probe Testing. The median value of the distal Euler-Byrne score was 143.5 in responders (interquartile range, 77 to 197) and 47.5 in nonresponders (interquartile range, 36 to 101; p = .006; Fig 1). The positive predictive value of the Euler-Byrne score was 92.7%, and the negative predictive value was 46.2%, according to the established abnormal value of 50.

The median time that the distal pH was less than 4 was 6.3% in responders (interquartile range, 4.5% to 10.5%) and 3.1% in nonresponders (interquartile range, 2.7% to 4.7%; p = .004; Fig 1). The positive predictive value of the time the distal pH was less

Fig 2. Tracings from distal pH probe studies completed in A) March 1995 and B) March 1996 in 9-year-old girl with chronic cough, recurrent pneumonia, and sore throat. Note poor reproducibility of study. Euler-Byrne score increased from 8 to 248, and percent time distal pH was less than 4 increased from 0.2% to 4.5%. Therapy with proton pump inhibitor and Propulsid, initiated after second pH probe study, resulted in marked improvement.



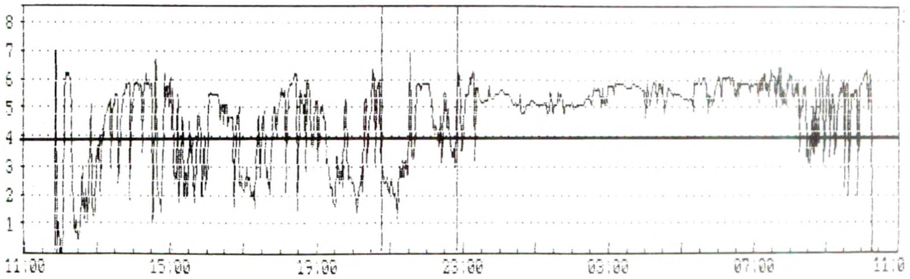


Fig 3. Distal pH probe tracing obtained from 4-year-old boy with chronic cough, recurrent sinusitis, bronchitis, and otitis media while receiving therapy with proton pump inhibitor and omeprazole. Because of persistent reflux events and lack of clinical response to antireflux therapy, patient subsequently underwent 270° fundoplication and experienced improvement in his symptoms.

than 4 was 97.4%, according to the established abnormal value of 5%, and the negative predictive value was 30%. The median and mean number of prolonged events lasting more than 5 minutes did not vary between the responders and the nonresponders (3 events per study versus 1 event per study, respectively; $p > .05$).

Gastrointestinal Symptoms. The presence of gastrointestinal symptoms did not predict the response to antireflux therapy in patients with extraesophageal manifestations of GERD. Gastrointestinal symptoms were absent in 24 of the 58 patients (40%) who responded to therapy. Gastrointestinal symptoms were present in 6 of the 10 patients (60%) who did not respond to therapy ($p < .05$; Table 2).

Reproducibility of pH Probe Results. Seven patients underwent repeat pH probe testing while not on therapy. The results changed from normal to abnormal in 4 patients (Euler-Byrne score, 2; 2% of time with a distal pH less than 4; Fig 2). More aggressive medical antireflux therapy resulted in improved symptoms in 2 patients; a 270° fundoplication resulted in a cure in 1; and in the remaining patient, the follow-up has been inadequate to assess the response.

Distal pH Probe Testing for Evaluating Efficacy of Antireflux Therapy. Eight patients underwent repeat distal pH probe testing on antireflux medications or after fundoplication. The events of GER were adequately controlled in 3 patients on pharmacological therapy and in 2 patients after fundoplication. Persistent reflux was noted in 3 patients, and 2 experienced improvement after more aggressive medical antireflux therapy (1) or surgical therapy (1; Fig 3). The symptoms in the remaining patient were unchanged despite institution of additional medical therapy.

Double-Probe pH Testing. Double-probe pH studies were completed in 13 patients. The pH was less than 4 between 1% and 9.6% of the time (mean, 2.6%). Antireflux therapy resulted in a cure in 5 patients and an improvement in 7 patients. One patient (pH less than 4 for 1.5% of study time) remained unchanged after initiation of antireflux therapy. Of note, the percentage of time the distal pH was less than 4 was normal in 3 of these patients, 2 of whom improved with antireflux therapy.

One patient demonstrated the unique finding of a

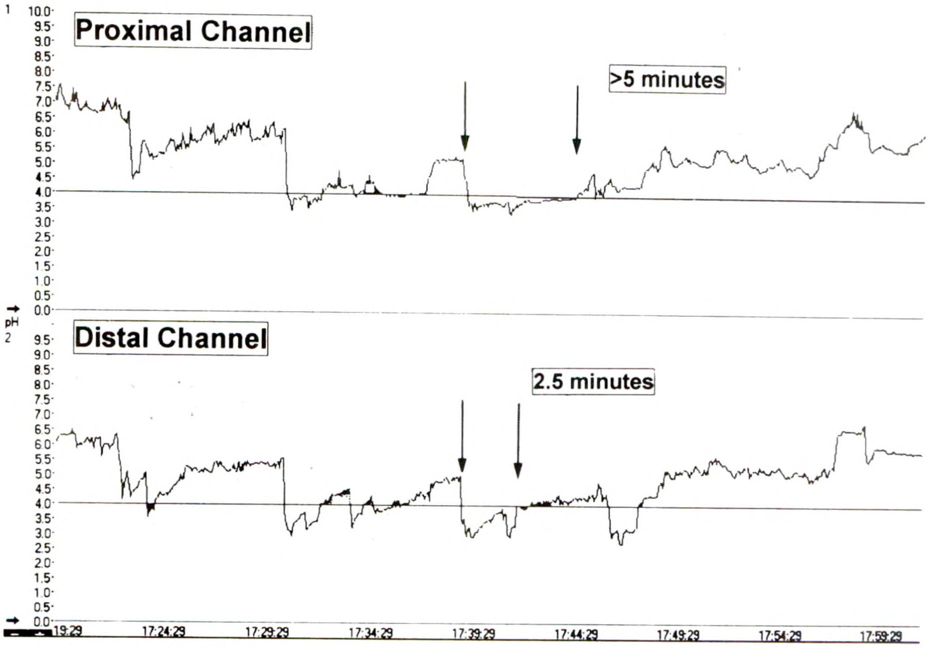


Fig 4. Double-probe pH tracing in 11-year-old girl with hoarseness and true vocal cord nodules. Note varied rate of clearance of simultaneous reflux event reaching upper esophageal probe compared with that reaching lower esophageal probe (arrows). Mucosa of upper esophagus may not be as effective in clearing reflux events as that of lower esophagus.

prolonged reflux event at the upper probe (5 minutes) with a simultaneous short reflux event at the distal probe (2.5 minutes), suggesting that clearance of the acidic event in the superior esophagus was not as efficient as that in the distal esophagus (Fig 4).

DISCUSSION

Establishing GER as a cause or exacerbating factor of extraesophageal disease is a diagnostic challenge. Although distal pH probe testing is considered the "gold standard" for diagnosing reflux events as a cause of gastrointestinal manifestations, it is not the ideal study for detecting reflux as a cause or exacerbating factor of extraesophageal symptoms. The predictive value of distal pH probe testing is quite high, according to both the Euler-Byrne score (92.7%) and the percentage of time the pH is less than 4 (97.4%). These findings indicate that patients with an abnormal distal pH probe test result are likely to respond to antireflux therapy. Unfortunately, the negative predictive value of distal pH probe testing is poor (46.2% for the Euler-Byrne score; 30% for the percentage of time the distal pH is less than 4). This finding explains why many patients in this series still responded well to antireflux therapy despite having a normal result on the distal extended pH probe study.

The reproducibility of pH probe results in the small subset of patients who underwent multiple studies was poor, despite a monitoring period of 16 to 24 hours. The poor negative predictive value and the poor reproducibility of distal pH probe testing support the use of an empiric trial of antireflux therapy in patients in whom GERD is a suspected cause or exacerbating factor of extraesophageal symptoms. Therapy with a PPI has great efficacy in reducing acid production and is administered daily or twice daily. Although PPIs are not approved for use in pediatric patients by the US Food and Drug Administration, serious side effects from them are uncommon. Prolonged use at extremely high doses induced gastrinomas in rats, but this complication has not been reported in humans.[12] Dosing in pediatric patients who weigh less than 30 kg is generally started at 1 mg/kg per day, although higher doses are often necessary to achieve complete acid suppression.[13]

If symptoms persist unabated despite PPI therapy, a promotility agent such as metoclopramide or Propulsid may be added to the treatment regimen. If symptoms still persist, a pH probe study should be performed with the patient on a PPI and a promotility agent to evaluate the adequacy of therapy.

The poor correlation between antireflux therapy and the presence of gastrointestinal manifestations of GERD underscores the inability to predict by history which patients will benefit from antireflux therapy. More patients underwent pH probe testing for evaluation of extraesophageal symptoms than for evaluation of gastrointestinal manifestations in this series. This trend likely reflects the tendency of our pediatric gastroenterologists to empirically treat patients with gastrointestinal symptoms without a pH probe study. The poor negative predictive value of distal pH probe testing in this series supports a similar approach to the management of patients with extraesophageal symptoms until better diagnostic criteria are established.

Because esophageal clearance of refluxate lessens during sleep, nocturnal distal reflux has been considered particularly significant.[14] However, most patients in this series who responded to therapy experienced more daytime reflux than nighttime reflux — a unique distinction between gastrointestinal and extraesophageal symptoms of GERD. Although prolonged episodes of distal reflux are thought to be more contributory to gastrointestinal manifestations of GERD than are frequent, short reflux events, this association was not noted in our patient population.

It is possible that double-probe or triple-probe pH testing[15] will prove a better diagnostic tool for establishing GER as a cause or exacerbating factor of extraesophageal manifestations. The value of double-probe pH testing is limited by the lack of a prospective randomized study establishing pathological scores. Some investigators consider 1 reflux event to the superior esophagus to be abnormal,[16,17] and others consider more than 1% of the study time with a pH of less than 4 to be pathological,[7] but these values are not based on prospective studies assessing the outcome of treatment. All of the patients in this series who underwent double-probe pH studies had a pH of less than 4 in the superior esophagus for more than 1% of the study time; only 1 failed to respond to antireflux therapy. These results preclude calculating the predictive value of double-probe pH testing.

To further complicate the diagnostic challenge, extraesophageal symptoms can arise either directly, from upper esophageal irritation, or indirectly, from irritation of sensory (afferent) neurons in the distal esophageal mucosa in the absence of superior reflux events. This last mechanism has been demonstrated by the modified Bernstein test in patients with chronic cough, apnea, stridor, and reactive airway disease. Hydrochloric acid applied to the distal esophagus may elicit bronchospasm in asthmatic individuals,[6] stridor in infants,[18] and even obstructive and central apnea[4] in the absence of pharyngeal stimulation. Chemonociceptive stimulation of the distal esophageal mucosa in dogs also has been shown to induce life-threatening obstructive and central apnea.[19]

This review is somewhat limited by its retrospective nature, particularly because antireflux therapy was not standardized in the patients before determining their response to therapy. Some patients underwent a trial of H2 receptor antagonists alone or in combination with a promotility agent, whereas other individuals received a PPI alone or in combination with a promotility agent. Patients in whom medical therapy was deemed to have failed underwent a 270° fundoplication.

Patients who were either cured or improved with antireflux therapy were considered "responders." Several factors could account for the variability in degree of response. First, the response to therapy was judged by the patient's caretaker; second, the antireflux pharmacological regimens have various degrees of therapeutic efficacy; and last, extraesophageal symptoms of GERD often have multifactorial causes. For instance, patients with chronic cough often have reflux during the cough due to the marked increase in intra-abdominal pressure. Repeated reflux events such as this may irritate afferent vagal nerve endings in the distal or proximal esophagus and induce cough events, thus exacerbating the underlying condition. Reducing the acidity of refluxate with pharmacological therapy may eliminate the component of the cough exacerbated by reflux and cause an improvement in symptoms. We also may have underestimated the incidence of extraesophageal symptoms, especially with respect to sinusitis, because no patients were directly questioned regarding a history of recurrent acute or chronic sinusitis.

The high percentage of patients in this series who responded to antireflux therapy supports the continued study of GER as a cause of extraesophageal disease in pediatric patients. A prospective, randomized, placebo-controlled trial using double-probe pH studies is warranted.

CONCLUSIONS

Antireflux treatment in pediatric patients who were thought to have extraesophageal symptoms of GER resulted in an improvement or cure in 85% of subjects in this study. The presence or absence of gastrointestinal symptoms did not predict the response to antireflux therapy. The positive predictive value of distal pH probe testing was greater than 90%, according to the established criteria of the Euler-Byrne score or the percentage of time that the pH was less than 4. The negative predictive value of distal pH probe testing was poor (less than 50%), as was the reproducibility. These findings support an empiric trial of antireflux therapy in pediatric patients in whom extraesophageal symptoms of GERD are suspected until a prospective, controlled study is performed to better evaluate double-probe pH testing in these patients. Patients who fail to improve with conservative and pharmacological therapy should undergo double-probe pH testing while on medical therapy to determine whether GER is adequately controlled. Surgical therapy is necessary in some patients to achieve control of reflux.

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ENDOSCOPIC EVALUATION OF SWALLOWING AS AN ALTERNATIVE TO 24-HOUR PH MONITORING FOR DIAGNOSIS OF EXTRAESOPHAGEAL REFLUX

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Patients with symptoms of extraesophageal reflux may not be eager to undergo 24-hour pH probe monitoring for the sake of a definitive diagnosis. It has been anecdotally noted that extraesophageal reflux can be detected during an endoscopic swallowing evaluation. The purpose of this pilot study was to demonstrate that flexible endoscopic evaluation of swallowing with sensory testing (FEESST) can be implemented to identify and subsequently treat patients with extraesophageal reflux. Over a 6-month period, FEESST was prospectively performed in 20 healthy control subjects and in 20 patients with dysphagia. The dysphagic patients did not have a history of stroke or chronic neurologic disease. Attention was specifically directed toward noting the presence or absence of reflux into the laryngopharynx during the endoscopic swallowing evaluation. None of the control subjects were noted to have reflux during FEESST, but 18 of the 20 patients with dysphagia were found to have reflux during the evaluation; this difference was statistically significant ($p < .001$, Fisher's exact test). We conclude that FEESST is useful as a means of diagnosing extraesophageal reflux in patients with dysphagia.

KEY WORDS — endoscopy, gastroesophageal reflux, pH, swallowing.

INTRODUCTION

Extraesophageal reflux (EER) is an extremely common and potentially debilitating disease that is increasingly receiving more attention.[1] Traditionally, the diagnosis of EER is made by a combination of history-taking, physical examination, and diagnostic instrumentation testing. Currently, double-probe 24-hour pH monitoring in conjunction with barium esophagography is considered to be the most sensitive and specific method of making a diagnosis of EER.[2] However, the sensitivity of pH probe monitoring and esophagography is, at best, 80%.[2] Further, many patients are reluctant to have any type of foreign body in the nose and laryngopharynx for 24 hours.

Over the past decade, endoscopic evaluation of swallowing has emerged as a less expensive, nonradioactive alternative to a modified barium swallow study for the diagnosis and management of dysphagia.[3,4] One of the distinct advantages of endoscopic evaluation of swallowing is the ability to clearly observe topographic changes in both laryngopharyngeal mucosal thickness and color, features not seen on videofluoroscopy. In addition, it has been noted that EER can be readily detected during endoscopic swallowing evaluations.[5] Further, the recent development of a quantitative method of evaluating laryngopharyngeal sensitivity during an endoscopic swallowing evaluation — called flexible endoscopic evaluation of swallowing with sensory testing (FEESST) — may be useful not only in documenting EER, but also in quantifying the arytenoid edema so often noted during fiberoptic examination of the larynx in patients with EER.[6,7] Laryngopharyngeal sensation is determined by delivering discrete pulses of air to the laryngopharyngeal mucosa to elicit the laryngeal adductor reflex.[8,9] The purpose of this pilot study was to determine whether FEESST is useful for detecting EER in a cohort of patients with dysphagia.

MATERIALS AND METHODS

Twenty patients with dysphagia and 20 healthy control subjects were prospectively evaluated over a 6-month period. None of the test subjects were cigarette smokers. The dysphagia group consisted of 12 women and 8 men with a mean age of 64.3 years (SD, 21.4 years; range, 32 to 95 years). The dysphagia group did not have a history of stroke or chronic neurologic disease and were ambulatory outpatients without a history of vocal fold paralysis or tracheostomy. Dysphagia was defined as any subjective or objective difficulty handling food or secretions, or coughing or choking during ingestion of solid or liq-

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uid food. The control group consisted of 5 women and 15 men with a mean age of 40 years (SD, 11.5 years; range, 30 to 70 years) without any history of laryngopharyngeal complaints, reflux symptoms (heartburn, regurgitation), or prescription antacid use in the 6 months before the study.

A detailed history was obtained from each individual in the study, focusing on the presence or absence of the following symptoms: dysphagia and/or globus sensation, throat-clearing, heartburn and/or indigestion, increased phlegm, and cough. Both groups of subjects subsequently underwent FEESST. The FEESST protocol has been described in detail previously.[5] Initially, an endoscopic examination of the larynx was performed. Attention was specifically directed toward the presence or absence of the following findings: 1) posterior commissure hypertrophy and/or interarytenoid edema, 2) arytenoid edema, 3) arytenoid erythema, and 4) vocal fold edema. Posterior commissure hypertrophy and/or interarytenoid edema was defined as edema either obliterating the concavity of the posterior commissure or creating a convexity or obstruction of the posterior commissure. Arytenoid edema was defined as obliteration of the mucosal protuberance of the cuneiform and corniculate cartilages together with thickening of the mucosa at the site at which the aryepiglottic fold joins the arytenoid. Arytenoid erythema was defined as redness of the arytenoid mucosa relative to the surrounding laryngopharyngeal mucosa. Vocal fold edema was defined as loss of vocal fold sharpness together with polypoid changes to the vocal fold mucosa.

Subsequent to the flexible laryngoscopy, laryngopharyngeal sensory discrimination testing was carried out by endoscopically delivering 50-ms pulses of air to the mucosa just anterior to the arytenoid while varying the pressure intensity of the air pulse. The air pulse pressure ranged from 2 to 10 mm Hg and was delivered from an air pulse stimulator and endoscope made especially for this purpose (Pentax Precision Instrument Corp, Orangeburg, NY). The same endoscope was used to perform the laryngopharyngeal endoscopic examination, sensory testing, and swallowing evaluation. As described in earlier work, the laryngopharyngeal sensory discrimination thresholds in this study were defined as normal (less than 4.0 mm Hg of air pulse pressure), moderately impaired (4.0 to 6.0 mm Hg of air pulse pressure), or severely impaired (less than 6.0 mm Hg of air pulse pressure). Pressure application other than air pulse pressure, pain threshold determination, and alteration in pH were not used to stimulate the laryngopharynx.[5,7,9]

After the sensory testing procedure was performed, 5 teaspoons of applesauce were given and 5 swallowing parameters were examined in detail: 1) spillage, defined as entry of the head of the food bolus into the hypopharynx more than 1 second before the swallowing response occurred; 2) pharyngeal residue or pooling, defined as persistence of material (barium or green food coloring) along the pharyngeal walls or within the pyriform sinuses or valleculae; 3) laryngeal penetration, defined as passage of material into the larynx that does not pass below the vocal folds; 4) aspiration, defined as passage of material below the level of the true vocal folds into the trachea; and 5) reflux, defined as passage of material from the esophageal inlet retrograde into the laryngopharynx before, during, or after the swallow. All examinations were recorded on videotape.

All patients who were noted to have reflux during the FEESST were subsequently placed on an antireflux regimen that included dietary and positional changes (reflux precautions) and a course of proton pump inhibitor therapy.

Fisher's exact test was used to assess the statistical significance of the difference between the two groups.

RESULTS

Control Group. None of the control group reported any laryngopharyngeal symptoms. On flexible laryngoscopy, 1 control subject had interarytenoid and arytenoid edema and bilateral moderate laryngopharyngeal sensory deficits. Another control subject had edema of the vocal folds. None of the control subjects demonstrated laryngopharyngeal reflux during the FEESST.

Dysphagia Group. In addition to the complaint of dysphagia (100%), the symptoms most frequently described were cough (60%), throat-clearing (35%), phlegm (35%), and heartburn (15%). Interarytenoid edema was seen in all 20 dysphagic patients, with arytenoid edema noted in 17, arytenoid erythema in 9, and vocal fold edema in 3. Laryngopharyngeal reflux was seen in 18 of the 20 patients, and bilateral moderate-to-severe laryngopharyngeal sensory deficits were detected in 15 patients.

The difference in reflux findings between the two groups was significant ($p < .001$, Fisher's exact test). There also was a significant difference in the incidence of sensory deficits in the dysphagia group relative to the control group ($p < .001$, Fisher's exact test).

DISCUSSION

Although chronic cough and frequent throat-clearing are the more common presenting symptoms of patients with EER, patient complaints of difficulty swallowing or having a sensation of something stuck in the throat are also often described.[1,2,6,10] The purpose of focusing on a cohort of non–neurologically impaired patients with dysphagia was to necessarily select a group of patients who were particularly symptomatic. This study indicates that EER can readily be detected with an endoscopic evaluation of swallowing in dysphagic patients without a history of stroke or chronic neurologic disease. Our endoscopic study of control subjects also corroborates Koufman's[10] 24-hour double-probe pH monitoring of healthy subjects, in whom EER did not appear to take place.

Recent studies on EER have demonstrated that edema of the larynx, not erythema, is the hallmark of laryngopharyngeal reflux.[2,6] This pilot work supports these descriptions of EER and goes a step further by beginning to quantify the laryngopharyngeal edema that is seen during endoscopic swallowing evaluations in patients with EER.

Future work will focus on the relationship between laryngopharyngeal sensory deficits and laryngopharyngeal reflux in large numbers of patients, as well as a study of the application of FEESST to detecting laryngopharyngeal reflux in a cohort without complaints of dysphagia.

CONCLUSION

In patients with complaints of dysphagia who do not have a history of neurologic disease, FEESST appears to be a simple, reliable method of detecting EER.

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